HEART BLOCK FOLLOWING DIPHTHERIA

BY

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From the Royal Northern Infirmary, Inverness

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In 1943 when reporting a case of congenital heart block with dextrocardia (Leys, 1943) I discussed the differential diagnosis of acquired and congenital heart block. It was remarked that complete heart block due to diphtheria (and probably other infections also) was almost always fatal, and that nearly all cases of complete heart block in children and young adults were congenital. Fishberg (1940) with his very extensive practice, had seen only one patient surviving the appearance of complete heart block in diphtheria: he referred to a study by Stechner in 1928 of 19 cases, all fatal, and to a study by Jones and White in 1927 of 100 patients after severe diphtheria, none of whom had evidence of heart disease at the time of their examination. Hoskin (1926) found various minor post-diphtheritic cardiographic changes in 16 cases following severe attacks, but found no conduction defects.

I now report a case of complete dissociation of auricle and ventricle in a married woman of 25 who had severe diphtheria at the age of 10 with palatal and ocular palsies. She reports that her heart was said to have been affected at that time, and that it was later remarked to her, when she had cerebrospinal fever at the age of 22, that she had a slow pulse. No comment on her pulse rate was made when she had appendicectomy at a cottage hospital at the age of 18.

She was referred to the Royal Northern Infirmary, Inverness, because of attacks of syncope; these had began to appear shortly after an illness in which she had sore throat and joint pains. She remained in bed for only a few days. A similar illness had occurred two years previously. The attacks consisted of a choking sensation in the throat, pain and a tight sensation in the chest, followed by transient loss of consciousness, and later by vomiting.

The heart rate at rest is either 36 or 48; other rates are not found. After exercise it rises

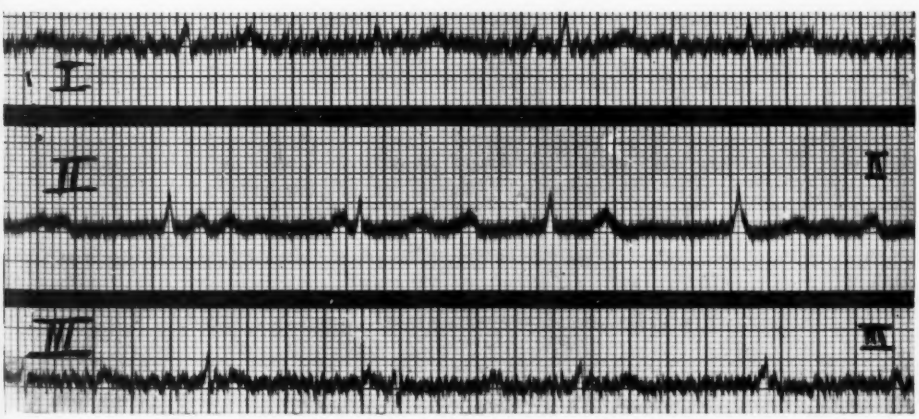

FIG. 1.—Electrocardiogram, showing complete heart block: auricle, 86; ventricle, 60 a minute; after exercise.

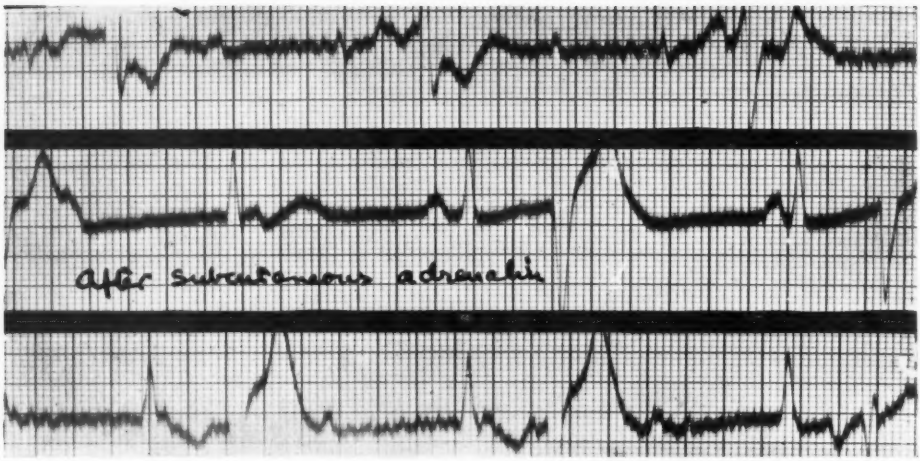

FIG. 2.—After subcutaneous injection of adrenalin showing frequent ventricular extrasystoles: auricular rate about 75; ventricular rate about 48 when no extrasystoles.

to 60. It is not influenced by subcutaneous injection of 1/100 of a grain of atropine sulphate. Ventricular extrasystoles appear after exercise and after subcutaneous injection of adrenalin. These extrasystoles alternate with regular beats for 10 to 20 cycles at a time. X-ray screening shows slight enlargement of the left side of the heart. Clinically, the heart does not appear enlarged, with the apex beat three and a half inches from the midline. There are no murmurs. The blood pressure is 150/90. The pulse is dicrotic. The cardiogram shows complete dissociation of auricle and ventricle, but otherwise is normal except for the appearance of the ventricular extrasystoles. These are not present when she is at rest. There is a complete absence of all tendon jerks throughout the body.

SUMMARY

The evidence for this case of complete heart block being due to diphtheria is:

(1) that she had severe diphtheria with neuritis at the age of 10 years;
(2) that subsequently a slow pulse was reported at the age of 22 years; and
(3) that she has complete absence of all tendon jerks without other evidence of nervous system disease.

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AURICULAR FIBRILLATION AND AURICULAR FLUTTER IN DIPHTHERIA

BY

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Auricular fibrillation and auricular flutter are generally regarded as uncommon heart disorders in children—a fact that is illustrated by their omission from many textbooks of pædiatrics. Auricular fibrillation develops in mitral stenosis due to rheumatic involvement of the heart, when it appears generally after the age of puberty; but it can occur in children of all ages in the course of a severe acute infectious disease, especially diphtheria. The reports of auricular fibrillation and auricular flutter occurring in diphtheria are not numerous: Burkhardt (1938) could not detect one case of auricular fibrillation amongst 140 cases of diphtheria examined electrocardiographically every second or third day; Bourne (1941) described one case of diphtheritic myocarditis with auricular flutter in a woman aged 79 years; Campbell *et al.* (1943) reported a case of transient auricular fibrillation in a youth of 22 years. Another report, Neubauer (1942), recorded three cases of auricular fibrillation in a series of 100 cases of diphtheritic heart disorders in children.

Altogether 6 cases of auricular fibrillation among a series of 200 cases of diphtheritic myocarditis have now been observed between June, 1941, and June, 1944, that is an incidence of 3 per cent. It occurred in 5 children and 1 adult: their ages were 2 years and 5 months, 2 years and 9 months, 6, 8, 10, and 28 years. The auricular fibrillation was associated with severe myocarditis and in all cases an involvement of the conducting system was found by cardiographic records. Partial auriculo-ventricular block was found in four patients and complete block in the other two, whose ages were 2 years and 5 months, and 6 years. The heart action was found slow (40–75 a minute) and irregular in partial A-V block and slow and regular in complete heart block. Examples are given in Fig. 1 and 2. The chief clinical signs observed were as follows:

	Cases		Cases
Syncope	2	Engorged jugular veins	2
Vomiting	4	Enlarged liver	2
Cyanosis	3	Severe albuminuria	4
Enlarged cardiac dullness	4		

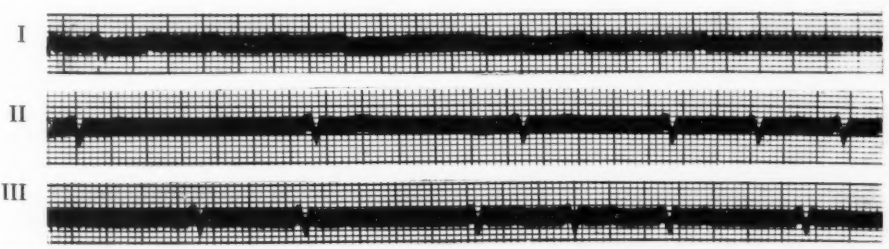

FIG. 1.—An example of auricular fibrillation with slow ventricular rate. The ventricular rate is about 50 a minute. QRS is of low voltage; S–T–T is almost isoelectric. The slow ventricular rate indicates some degree of partial A-V block. (D. E., 2 years and 9 months old, twelfth day of diphtheria.)

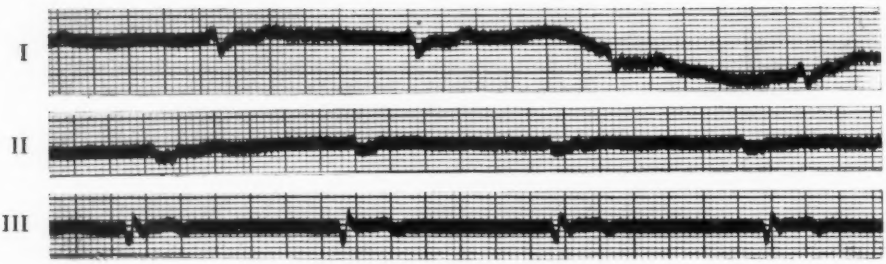

FIG. 2.—An example of auricular fibrillation with complete A-V block. The ventricular rate is about 49 a minute, regular. QRS is splintered and notched, of Q-type in lead III, and of low voltage, with a duration of 0·14 sec. T is small in leads I and II and inverted in lead III. (J. W., 2 years and 5 months old, eleventh day of diphtheria.)

The blood pressure was diminished in all instances, and the lowest readings were 56/30 in the child 10 years of age. Four patients died, two recovered. The adult made a complete recovery from a partial A-V block: she developed palatal, pharyngeal, facial, and hypoglossal paralysis and peripheral neuritis of the legs in the course of the disease and she was discharged after three and a half months. The other patient who recovered was the girl of six with complete heart block, palatal and pharyngeal paralysis, and peripheral neuritis of the legs; she was discharged with no clinical signs present in her heart and with an almost normal cardiogram after three months. The death occurred in one patient 2 years and 5 months old (Fig. 2) on the eleventh day of disease; two children, 2 years and 9 months and 8 years of age, died on the sixteenth day of disease, and another patient of 10 years died on the forty-fourth day of the disease.

To supplement the limited number of reports on auricular fibrillation and auricular flutter in childhood, the following account of a case is given, with clinical, cardiographic, and pathological findings.

History. L. A., aged 5 years. Previous diseases; chicken pox in 1941 and measles in 1943. The child had not been inoculated against diphtheria. On May 12, 1944, she began to vomit, developed a sore throat and a slight croupy cough, and was admitted to hospital two days later.

On admission the picture was not one of a very ill child. Examination revealed the presence of œdema in the throat and membrane covering both tonsils; enlarged cervical glands and oral fœtor were noted. A bacteriological examination of the throat swabs showed the presence of *C. Diphtheriæ* and *S. Hæmolyticus*. The child was given 20,000 units of diphtheria antitoxin. A regular tachycardia was present at this stage, the heart sounds being normal.

The course of the disease was as follows:

May 18 (7th day of the disease). A punctate rash appeared on the trunk, the throat was highly inflamed, and the tongue was peeling at the tip and on the edges.

May 20. Severe albuminuria, a sign of bad prognosis, manifested itself. Tachycardia persisted.

May 21. Red strawberry tongue. The first apical heart sound was found to be diminished in intensity; the pulse rate was 124 and the blood pressure 65/35. The child was restless and the general condition had deteriorated, the colour being poor. Blood sedimentation rate 21 in the first hour.

May 24. The child presented some cyanosis of the lips and distended jugular veins. The pulse was weak and irregular, the rate varying between 136–150. The heart action was irregular, the rate being 160–180 (Fig. 3).

May 25. Her condition was progressively worse. The pulse was soft, with a rate of about 160 (Fig. 4). The abdomen was slightly distended and the liver dullness increased.

May 26. The heart action appeared to be regular and the rate slower. The blood pressure was 85/50, but the child was very restless and seemed to be having pain in the precordial region. The cardiographic findings were similar to those demonstrated in Fig. 4 showing auricular flutter with 2 : 1 block.

May 27 (16th day of disease). The child died.

Post-mortem findings (Professor Bernard Shaw). Heart weighs 104 grams. The pericardial sac contains a normal amount of free fluid. There is no pericarditis. The right auricle is slightly dilated and contains post-mortem thrombus. The foramen ovale is closed. The tricuspid valve admits two fingers and the cusps are thin and delicate. The right ventricle is not dilated, the muscle

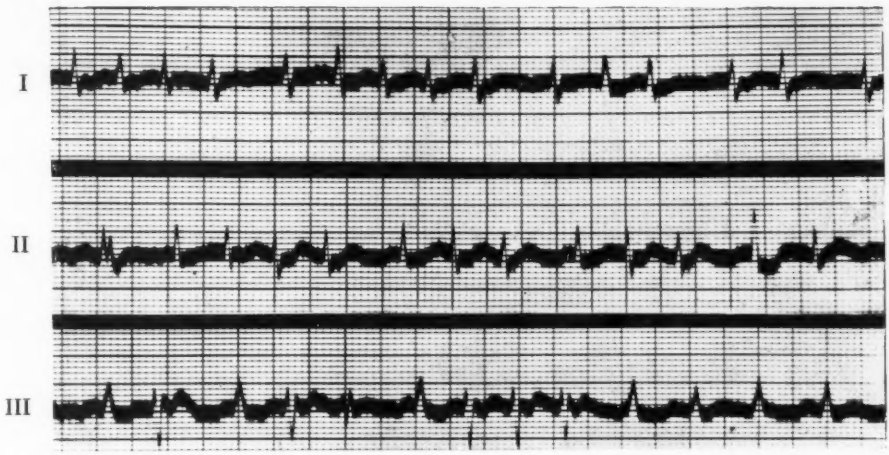

FIG. 3.—Auricular fibrillation. Heart action irregular. Rate about 180 a minute. No P waves are visible. Fine undulations between the ventricular deflections, irregular in timing, voltage, and contour. (See text.)

FIG. 4.—Auricular flutter with irregular block, 2 : 1 and 1 : 1. There are continuous regular flutter waves (F), best seen in lead II and III, occurring at the rate of 260 a minute. The ventricular rate is generally just half as rapid, 130 a minute.

being 0·4 cm. in thickness at the base. The pulmonary artery is smooth and elastic. The left auricle contains post-mortem clot and the wall is slightly thicker than usual. The mitral valve admits one finger and the cusps and chordæ tendineæ are thin and delicate. The left ventricle is dilated and the muscle measures 0·9 cm. in thickness at the base. The aortic valve is normal. The aorta shows some hæmoglobin stain. The coronary arteries are patent and free from atheroma. The myocardium is pale; there are no hæmorrhages and no evident fatty changes.

Histology. Sections of right auricle, tricuspid valve, right ventricle, left auricle, mitral valve, and left ventricle: these sections show an acute myocarditis involving the musculature of both auricles and both ventricles, but more marked in the left auricle and left ventricle; with regard to the latter the lesions occur with equal frequency at all levels.

The lesions consist of multiple small cellular foci consisting of mobile histiocytes, a few polymorphs, and eosinophils, situated in the stroma, but with no evident relation to the vessels. The muscle fibres show no necrosis and no fatty change. Hidden in the bays between the columnæ carneæ of the right auricle are multiple mural ante-mortem thrombi probably induced by fibrillation.

The lesions might be due either to diphtheria or scarlatina as there is no histological differentiation between the two.

Discussion

On clinical and bacteriological grounds, the case was one of faucial diphtheria. Hæmolytic streptococci are not uncommonly found in diphtheritic throat lesions caused by *gravis* strain, and in the case under discussion the presence of hæmolytic streptococci, in addition to the development of a rash and strawberry tongue as described above, indicates beyond doubt a double infection. The persistent tachycardia and the diminished intensity of the first apical sound, the lowered blood pressure, and increased blood sedimentation rate were clinical manifestations of a myocarditis. Auricular fibrillation, detected clinically and cardiographically three days later, confirmed the presence of myocarditis; it persisted for two days in spite of digitalis therapy and ultimately changed to auricular flutter. Anatomical and histological findings at autopsy revealed an acute myocarditis with formation of ante-mortem mural thrombi.

Here, then, is an example of auricular fibrillation and auricular flutter developing as terminal events in the course of an extremely acute myocarditis.

It is with the kind permission of Professor Bernard Shaw that the detailed post-mortem notes are included with the present report.

My thanks are also due to Dr. I. E. McCracken, M.O.H., Newcastle upon Tyne, and to Dr. G. Hurrell, Medical Superintendent, City Hospital for Infectious Diseases, Newcastle upon Tyne, for facilities provided.

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HEART BLOCK AND THE SIMULATION OF BUNDLE BLOCK IN DIPHTHERIA

BY

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Cardiographic studies in diphtheria show that a wide variety of arrhythmias and abnormalities of pattern occur. Among these heart block is familiar, not so much because it is common, but because in its more severe forms it indicates a grave prognosis. Burkhardt, Eggleston, and Smith (1938) recorded 11 cases of A-V dissociation, all fatal; some presented a terminal ventricular tachycardia. They noted a high idio-ventricular rate of 80–90 so that block was not suspected before the cardiogram was taken.

Alstead (1932) found the P–R interval to exceed 0·2 sec. only once in 100 cases, although in 10 others this interval increased during the disease: two of his cases said to show complete block died; but the tracing of one of these is not convincing. Stecher (1928–29) studied 19 cases of complete block in diphtheria; all died. He publishes tracings of 11 cases; four of these show complete block, but of the remainder four show ventricular tachycardia and one normal rhythm with bigeminy. Nathanson (1928) described T wave changes in 7 cases, but noted no conduction changes; his Case 3 does, however, show a wide QRS. Friedemann (1932) found the ventricular rate high in complete block, but did not note so high a mortality as most other authors, in this condition. Begg (1937) had a mortality of 66 per cent in both bundle branch block and complete block. (One of his records said to show complete block, where the auricular rate is 100 and the ventricular 135, should perhaps be regarded as ventricular tachycardia.) Harries and Mitman (1941) state that partial block is rare, that left bundle block is commoner than right, and regard A-V block as a serious sign. On the other hand Neubauer (1942) found partial block in 17 per cent of cases (but his Fig. 10 described as showing 3: 1 block seems to show complete block) and complete block in 5 per cent. He also records auricular fibrillation associated with complete block. However, his Fig. 17 suggests complete block with normal auricular mechanism, not fibrillation; nor is auricular fibrillation evident as claimed in Fig. 14.

Present Investigation

Eighty-three cases of diphtheria were investigated clinically and serial cardiograms taken at intervals throughout the illness. About 300 cardiograms were taken in all, 2 or 3 in mild cases, more in the severe ones. In 63 of the patients the cardiogram was abnormal, that is in 76 per cent. Ten of these showed some defect of conduction; the others inversion of T in one or more leads; in less severe cases T was usually inverted in lead III only; in severe cases the inversion was seen in more than one lead, sometimes in all four. Displacement of the S–T segment was frequent, and nearly always downwards. Other abnormalities commonly seen were axis shift, slurring and slight widening of QRS, and bizarre P waves. Conduction changes were relatively uncommon; there was increase in the auriculo-ventricular conduction time in four, but in only one of these did it exceed 0·2 sec. In two of these there were also changes in the T waves. Bundle branch block with increase in P–R was recorded in three cases, and complete block in one: all these four patients died. Three other patients without block died, one during ventricular tachycardia, one from nervous lesions when his cardiogram had returned to normal, and one showing T changes and low voltage. The

mortality for the whole series was thus 8·4 per cent. There was no fatality over the age of 12, and none in an immunized subject.

Only ten cases are reported here, but they have been followed closely throughout their course in hospital, by the same observer, both clinically and cardiographically, and in all fatal cases necropsies were carried out and histological studies made.

Case Reports

Increase in P–R Interval

Case 1. J. R., age 7. Antitoxin on 8th day; pharyngeal and nasal diphtheria. 30th day, vomiting. 53rd day, palatal palsy. 83rd day, apparently quite well; EC. (electrocardiogram), N.R., rate 120; P–R, 0·18 sec.; T III just negative. 99th day, EC., N.R., rate 110; P–R, 0·15 sec.; T III flat. 111th day, EC., N.R., rate 90; P–R, 0·15 sec.; T III positive.

Case 2. M. D., age 18. Antitoxin on 7th day; pharyngeal diphtheria. 7th day, EC., N.R., rate 110; P–R, 0·16 sec. 13th day, EC., rate 75; P broad and bifid; P–R, 0·18 sec. 25th day, EC., N.R., rate 115; P–R, 0·2 sec. 32nd day, EC., N.R., rate 85; P broad and bifid; P–R, 0·18 sec. No complications in nervous system, nor clinical signs or symptoms of myocardial injury throughout.

Case 3. Mrs. G., age 24. Antitoxin on 6th day; pharyngeal diphtheria. 7th day, EC., N.R., rate 125; P broad and notched; P–R, 0·2 sec.; right axis deviation; B.P. 125/80. 60th day, EC., N.R., rate 65; P–R, 0·15; rate 100 with deep breathing; P–R increasing to maximum of 0·2 sec. No symptoms.

Case 4. J. G., age 8. Antitoxin on 6th day, immunized 18 months before; nasopharyngeal diphtheria. 8th day, EC. (Fig. 1A), N.R., rate 105; P–R, 0·15 sec.; slight depression of S–T in leads II and III. 22nd day; general condition good, no complications in nervous system; apex beat in mid-clavicular line fourth interspace; sounds normal at apex; wavy systolic pulsation to left of sternum in second and third interspaces; systolic murmur and second sound duplicated at pulmonary area; B.P. 95/55; liver edge three-quarters of an inch below right costal margin; EC. (Fig. 1B), N.R., rate 100; P–R, 0·2 sec., S–T depression in leads I, II, and IVR; elevation in III; T diphasic in II and IVR, negative in III. 32nd day, EC., N.R., rate 85; P–R, 0·2 sec.; T now positive in leads II

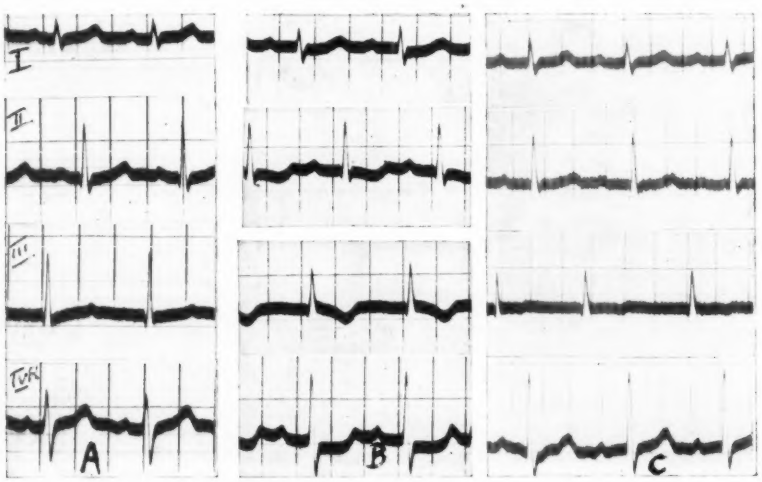

Fig. 1.—Case 4. Development of long P–R interval. (A) 8th day. (B) 22nd day. (C) 5 months later. See text.

and IVR and less negative in III; cardiac signs as before except that a faint blowing diastolic murmur was audible in the third interspace near the sternum. Discharged from hospital on the 80th day. On re-examination 3 months later, child seemed quite well; apex beat just outside mid-clavicular line; wavy precordial systolic pulsation; short rough diastolic murmur at apex in lying position; faint blowing diastolic murmur in third left interspace; B.P. 110/60; on radioscopy, pulmonary arc prominent, left ventricular contour slightly prominent, and left auricle not enlarged; EC., N.R., rate 90; P–R, 0·21 sec.; T III negative. The signs indicated that mitral stenosis and aortic incompetence were present and that rheumatic carditis had occurred some time before the attack of diphtheria. Examination 2 months later (5 months after discharge from hospital) showed no change in

physical or radioscopic signs; cardiogram (Fig. 1c) showed the P–R interval to be still 0·21 sec.; T inversion in lead III less and R in lead IVR of greater amplitude.

Prolonged P–R and Bundle Branch Block

Case 5. V. F., age 3. Antitoxin on 3rd day. Faucial diphtheria; B.P. 95/55. 7th day no clinical signs or symptoms of circulatory failure; B.P. 70/50; EC. (Fig. 2A), N.R., rate 105; P–R, 0·18 to 0·2 sec.; right bundle branch block (B.B.Bl.) but alternate beats in lead II show no B.B.Bl. 8th day vomiting and collapse. 9th day: B.P. 60/30; apex beat visible half an inch outside mid-clavicular line; heart sounds normal; liver edge one inch below right costal margin; EC. (Fig. 2B), N.R., rate 65; bundle branch block; P bifid or wavy; P–R, 0·3 sec. 11th day, died.

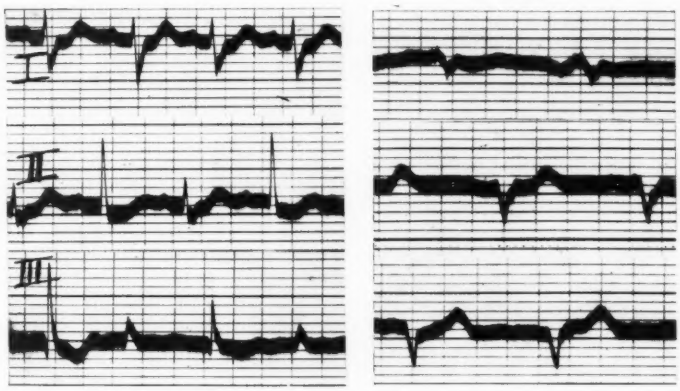

FIG. 2.—Case 5. Development of long P–R interval and bundle branch block. (A) 7th day. (B) 9th day. See text.

Necropsy. Left auricle contains adherent thrombus: on section, muscle fibres necrotic and œdematous. Right ventricle on section, degeneration of muscle; congestion and cellular infiltration. Left ventricle, on section, areas of advanced degeneration; some early fibrosis. Liver: intense venous congestion; necrosis in central part of lobules.

Case 6. A. G., age 12. Antitoxin on 2nd day (26 hours after onset). Faucial diphtheria, bull-neck, heavy albuminuria. 3rd day, apex beat difficult to feel, probably in mid-clavicular line; sounds normal; B.P. 95/70; EC. (Fig. 3A), N.R., rate 120, sinus arrhythmia; S–T depression in leads II and III; QRS, 0·07 sec.; P peaked in leads II and III, P–R, 0·12 sec. 8th day, swelling of neck almost gone; able to take light solid diet; palatal palsy; apex beat within mid-clavicular line, fourth interspace; systolic retraction in third left interspace; sounds normal; B.P. 80/60; liver not felt;

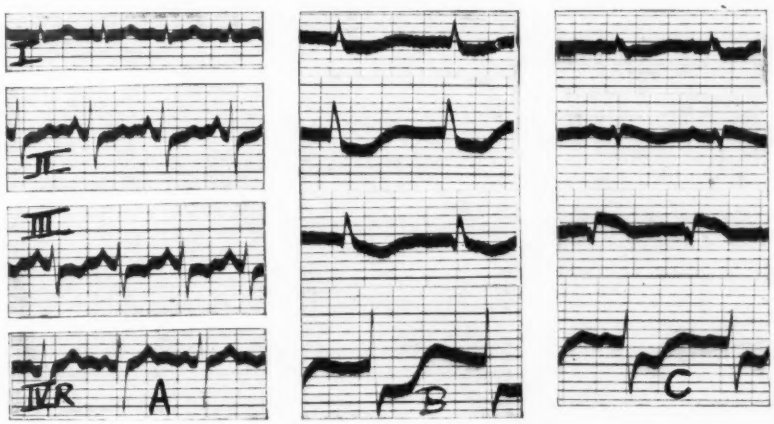

FIG. 3.—Case 6. Lengthening of P–R interval and widening of QRS complexes. (A) 3rd day. (B) 8th day. (C) 10th day. See text.

knee and ankle jerks present; EC. (Fig. 3B), regular rhythm rate 80; P wave not seen; QRS, 0·1 sec.; S–T depression in all leads. 10th day, vomiting; first sound very distant; second well heard; B.P. 70/60; jugular vein well seen, but not above level of second costal cartilage; liver not palpable; trace of albuminuria; EC (Fig. 3C), N.R., rate 90; P–R, 0·18 sec.; S–T deviation downwards in leads I and IVR, upward in II and III; QRS, 0·1 sec. Died suddenly two hours later after incision for intravenous infusion.

Necropsy. Heart: weight, 175 g.; left ventricle maximum thickness 1·2 cm., minimum 0·7 cm.; right ventricle, maximum thickness 0·5 cm.; 15 c.c. clear yellow fluid in right pleura, 7 c.c. in left pleura. On section, myocardium showed congestion, œdema, degeneration up to stage of necrosis, and cellular infiltration mainly with plasma cells, in all chambers, most in left ventricle; areas of intense congestion and cellular infiltration in pericardium. Liver: enlarged, edge reaching to within a quarter of an inch of umbilicus; on section, venous congestion, necrosis in central and mid-portions of lobules. Kidney: venous congestion; degeneration of tubular epithelium. Lung: areas of collapse and œdema separated by areas of emphysema.

Case 7. B. E., age 3. First antitoxin on the 5th day of the disease; faucial diphtheria. 6th day: apex beat fourth interspace not outside mid-clavicular line; sounds normal and well heard; B.P. 90/65; EC., N.R., rate 135, slight right axis deviation; P high voltage; P–R, 0·15 sec.; T III flat; T in IVR low voltage and diphasic. 7th day: triple rhythm at apex on inspiration; B.P. 90/70; EC. (Fig. 4A) as on previous day but rate 125. 9th day: triple rhythm at apex; B.P. 95/55; liver palpable and tender; slight dyspnœa; vomited once; heavy albuminaria. EC., N.R., rate 110; left bundle branch block; P–R, 0·18 sec. (Fig. 4B). 10th day, neck swelling almost gone; vomited once; apex beat not felt; triple rhythm at apex; B.P. 90/60. EC. (Fig. 4C), N.R., rate 110; L.B.B.Bl. but QRS altered since previous tracing; occasional supra-ventricular premature beat.

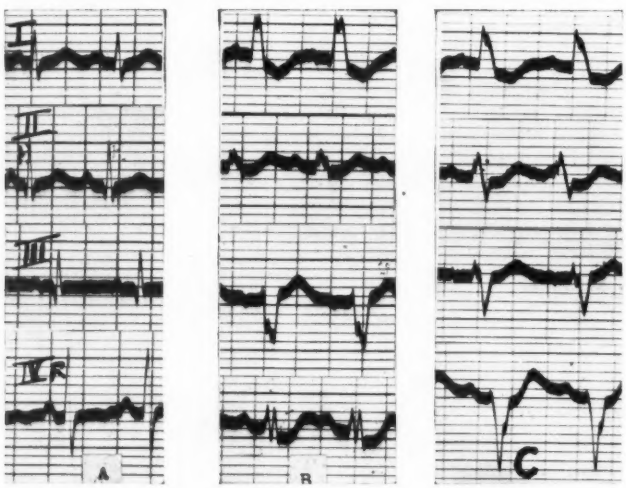

FIG. 4.—Case 7. Lengthening of P–R interval and development of bundle branch block. (A) 7th day. (B) 9th day. (C) 10th day. See text.

11th day, vomiting, pain over liver, which is increasing in size; apex beat fifth space within mid-clavicular line; triple rhythm not heard; B.P. 80/45; EC., N.R., rate 95; irregularity due to sinus arrhythmia, nodal escape and interference dissociation; P–R, 0·1 to 0·3 sec., L.B.B.Bl.: same day, 6.30 p.m., having intramuscular glucose-saline; B.P. 75/45; liver still larger; EC. similar to previous tracing but P flatter, and P–R up to 0·38 sec. 12th day: vomiting; nasal regurgitation; diffuse precordial pulsation; no apex beat palpable; shallow occasional sighing respiration; no signs in lungs; deep reflexes present; B.P. 65/45; EC. (Fig. 5), N.R., rate 90; sinus arrhythmia and nodal escape; bundle branch block of S type and of R type according to whether sinus or nodal rhythm is present; S–T depression in all leads. 13th day, vomiting, restlessness, pallor, constant sighing; apex beat not palpable, but visible in fourth and fifth interspaces and extending just outside mid-clavicular line; sounds distant; systolic murmur at apex; liver larger; B.P. 55/40, no signs in lungs. EC. (Fig. 6A), N.R., rate 105; P–R, 0·15 sec., bundle branch block of indeterminate type; 1/200 of a grain of atropine was given intramuscularly and ten minutes later the cardiogram had altered, becoming similar to the latter part of the tracing of the previous day; it shows nodal rhythm rate 92 and R.B.B.Bl. (Fig. 6B). Triple rhythm with audible third sound (Evans' type I B) was heard after the injection of atropine. 9.30 p.m., constantly sighing and crying out; radial pulse not palpable and B.P. not obtainable. EC. (Fig. 6C); nodal rhythm, rate 90; P not visible; R.B.B.Bl., QRS wider than in previous tracing; S–T depression all leads. Died two hours later.

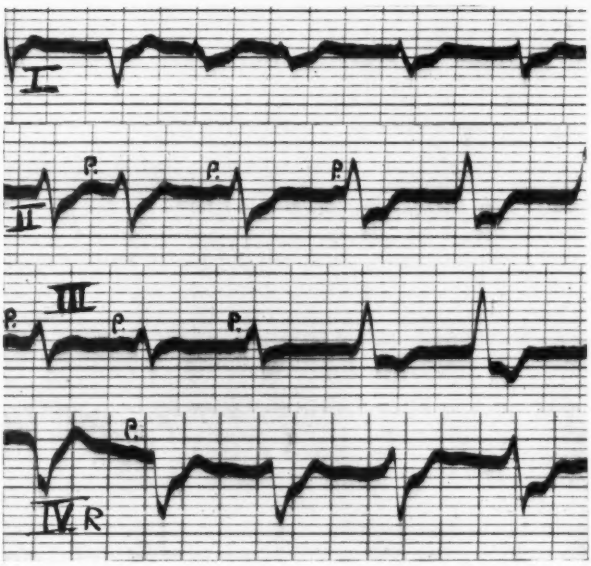

FIG. 5.—Case 7. Sinus arrhythmia and nodal escape with bundle branch block of varying type. 12th day. See text.

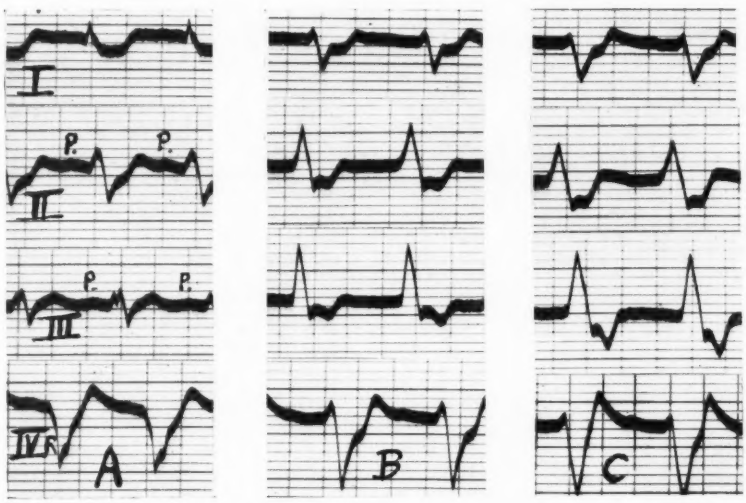

FIG. 6.—Case 7. Bundle branch block of varying type. All 13th day. See text.

Necropsy. Straw coloured effusions in both pleuræ, 450 c.c. in right, less in left; liver enlarged. Heart: weight 110 g.; left ventricle, maximum thickness 9 mm., minimum 3 mm.; right ventricle, maximum thickness 5 mm., minimum 2 mm.

Histology. Lungs: collapse, œdema and emphysema. Liver: marked venous congestion; advanced fatty degeneration; areas of necrosis. Heart: little normal muscle remains; advanced degeneration in all sections; areas of necrosis; œdema; a little fibrosis in left auricle and left ventricle.

Complete Heart Block

Case 8. M. L., age 8. First antitoxin on 3rd day; faucial and nasal diphtheria. 4th day: apex beat within mid-clavicular line; sounds normal; B.P. 100/50; EC. (Fig. 7A), N.R., rate 140,

right axis deviation; P–R, 0·1 sec.; slight S–T depression all leads. 6th day, vomiting and heavy albuminuria; apex beat in mid-clavicular line; sounds normal; B.P. 75/45; no liver signs; EC. (Fig. 7B) lead IVR only; rate 150; P–R, 0·15 sec., QRS, 0·12 sec. 8th day, vomiting blood; apex beat not palpable, sounds normal; petechiæ and ecchymoses in skin; EC. (Fig. 7C). Complete heart block, auricular rate 140 with sinus arrhythmia; ventricular rate 115; R.B.B.Bl.; S–T depression in all leads. 9th day, dyspnœa, vomiting; apex beat not felt; sounds normal; B.P. 60/0;

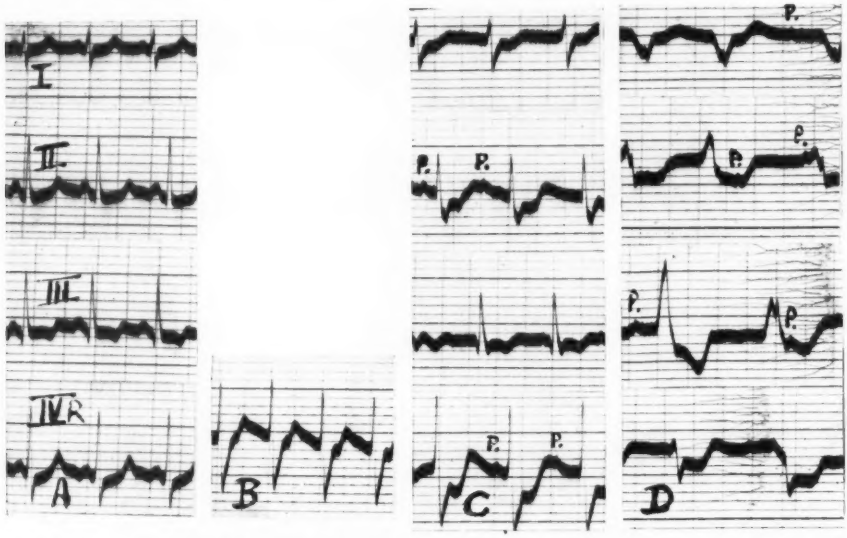

FIG. 7.—Case 8. Development of complete heart block and bundle branch block. (A) 4th day. (B) 6th day. (C) 8th day. (D) 9th day. See text.

EC. (Fig. 7D). C.H.B. with alternate ventricular extrasystoles; auricular rate about 126, ventricular rate about 90; R.B.B.Bl. Died 3 hours later.

Necropsy. Liver: some venous congestion, necrosis in centre of lobules; fatty degeneration. Lungs: congestion and small areas of collapse. Heart: weight, 110 g.; left ventricle, maximum thickness 12 mm., minimum 7 mm., pericardial and sub-endocardial petechial hæmorrhages; some plaques of atheroma in aorta just above aortic valve cusps, largest 3 by 5 mm.; on section, degeneration of muscle all chambers; areas of hæmorrhage into muscle; œdema slight; no cellular infiltration, no fibrosis.

Cases Simulating Bundle Branch Block

Case 9. J. P., age 8. Antitoxin given on 3rd day of disease. Diphtheria immunization 2 years previously. Mild tonsillar diphtheria; no abnormal cardiac signs; B.P. 100/50. 4th day: EC., N.R., rate 75; P–R, 0·18 sec., P diphasic. 13th day: EC., N.R., rate 85; P–R unchanged, P diphasic still, but increased in amplitude; T diphasic in leads II and III. 30th day: convalescent; no abnormal cardiac signs; EC. (Fig. 8), N.R., rate about 80; P diphasic; with sinus slowing "A-V nodal" escape beats appear with an upright QRS of 0·17 sec., depression of S–T and diphasic or positive T; in lead III a sinus rhythm only recorded; in lead II the fourth ventricular complex is preceded by a P wave with a P–R interval of 0·11 sec.; this QRS is intermediate in form between the QRS of the preceding "nodal" beats and the QRS of the following sinus beats; the last "nodal" beat in lead IVR is preceded by a negative P with a P–R interval of 0·11 sec. 32nd day: EC., N.R., rate 88; no sinus arrhythmia; and no "nodal" beats, otherwise tracing unchanged. Discharged well after 37 days in hospital. On re-examination 18 months later the child was quite well; no abnormal clinical signs; radioscopy: slight prominence of left middle arc; EC., N.R., rate 70; P–R, 0·18 sec., P of normal shape in limb leads, but diphasic still in IVR; ventricular complex physiological.

Case 10. C. T., age 10. Antitoxin on 4th day of illness; not immunized. Naso-pharyngeal diphtheria; severe toxæmia, bull-neck. 9th day: apex beat not palpable, sounds distant; EC. (Fig. 9), N.R., rate about 70; left axis deviation; S–T depression in lead I, T IV diphasic; in leads I and II the beats appear to originate in the A-V node, except for the last two beats in lead I and the last beat in lead II; in the "nodal" beats QRS is wide, S–T depressed, and T negative or diphasic, the pattern being similar to that seen in Case 9; in the last cycle but one in lead II QRS is preceded by a P wave with a P–R interval of 0·11 sec.; this QRS is intermediate in shape between the preceding "nodal"

FIG. 8.—Case 9. Nodal escape beats simulating bundle branch block. See text.

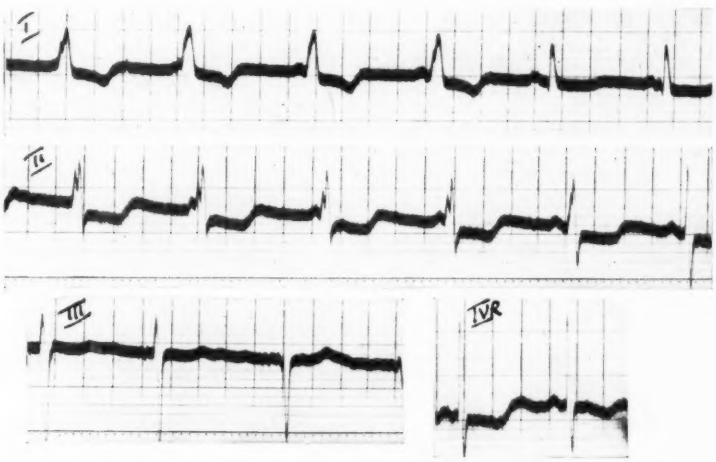

FIG. 9.—Case 10. 9th day. Nodal beats simulating bundle branch block. See text.

and succeeding sinus beat. 22nd day, palatal palsy and heavy albuminuria. 41st day: knee jerks absent, no abnormal cardiac signs; EC., N.R., rate 80, sinus arrhythmia; P–R, 0·12 sec.; T low voltage, and just negative in lead III. 53rd day, facial paralysis. 57th day: EC. N.R., rate 75; left axis deviation; T low voltage and just negative in lead III. Discharged from hospital on 124th day. On re-examination 7 months later, the child was quite well; no abnormal clinical or radioscopic signs; EC., normal rhythm, rate 70; left axis deviation, but QRS and T now of normal amplitude; and T III had become positive.

DISCUSSION

The histological studies in the four fatal cases show how intense are the degenerative changes in the myocardium in diphtheria and explain the variety of cardiographic changes recorded in the course of the disease.

Heart Block. An increase in conduction time between auricle and ventricle is not, as in rheumatic carditis one of the commonest manifestations of the myocardial injury, yet some interference with conduction was seen in all the cases with bundle branch or complete block (Cases 5–8) and there were in addition four cases in which an alteration in the P–R interval was the only indication of impaired conductivity .It is in the sub-acute phase of the disease, say after the eighth day, that a large proportion of cases show evidence of cardiac lesions and of systemic congestion, notably by an enlarged tender liver. At this time the heart rate is characteristically not increased and is often slow for a child; this relatively slow rate may conceal a defect in the conducting bundle which might be revealed at higher rates. The sinus bradycardia is another reason, in addition to the occurrence of high ventricular rates in complete block, why cardiography is essential for the diagnosis of block in diphtheria.

The single example of complete block in this series (Case 8) was found in an un-immunized girl aged 8, who had 36,000 of antitoxin intravenously and 40,000 units intramuscularly about 48 hours after the onset of symptoms. From the time of admission there was a progressive deterioration in the clinical condition, cardiograms showing S–T depression in all leads on the fourth day, increase in A-V conduction time and bundle branch block by the sixth day, and by the eighth day when she was vomiting blood and petechiæ were present in the skin, complete block with a ventricular rate of 115 was recorded. Before death on the tenth day the pulse had become slower and irregular due to complete block and alternate ventricular extrasystoles.

Bundle Branch Block. The records of this rhythm (Fig. 2–9), show that the pattern is not fixed but that rapid changes occur from day to day. A frank right bundle branch block picture was commoner than left, but low voltage, concordant, and "S" types and intermittent block were also seen. These quick changes suggest a rapidly extending lesion in the myocardium. But in Case 7 another factor behind these changes is seen, where the QRST pattern altered with the onset of nodal rhythm, both when this appeared spontaneously (Fig. 5), and when induced by an injection of atropine (Fig. 6B). This change may be compared with those to be discussed in connection with Cases 9 and 10. The usual discordant QRST pattern of bundle branch block shows reciprocal deviation of the S–T segment in leads I and III, but in most of the examples recorded here the S–T depression which is a characteristic and early change in toxic diphtheria is superimposed, resulting in S–T depression in all leads. A record from Case 6 taken in the terminal stage (Fig. 3C) does show reciprocal deviation of the S–T segment and is similar to that seen in acute cardiac infarction of posterior type. Studies of sections from this heart showed the most widespread degeneration to be in the posterior wall of the left ventricle with areas of almost complete necrosis.

Auricular Fibrillation and Auricular Flutter. Neither of these rhythms was encountered in any of the patients of this series.

Permanent Lesions. To establish the existence of permanent conducting lesions due to diphtheria it would seem necessary to have records showing the inception of the lesion during the disease. Such records are not always presented in published cases, but even so their number is few and it is generally accepted that however severe the lesions they clear up completely if the patient survives, and that to this rule exceptions are extremely rare. So far as branch block and complete block are concerned, no further light is thrown on this point by the cases reported here as all were fatal. But in one instance of latent block (Case 4) a prolonged P–R has persisted for five months, though the complication of chronic rheumatic carditis has to be taken into account. Moreover, persistence for five months is probably insufficient to classify a lesion as permanent.

Simulation of Bundle Branch Block. Two records were obtained (Cases 9 and 10, Fig. 8 and 9), showing abnormal ventricular complexes in beats arising in an ectopic focus, which at first sight suggest bundle branch block. In Case 10 they were discovered on the ninth day when the child was still seriously ill, but in the other on the thirtieth day when the patient was convalescent after a mild attack of the disease. In both instances QRS is wide enough to suggest bundle branch block, but the main deflections are upright and the increase in QRS is mainly due to prolongation of the proximal limb of R, the distal limb being little affected. Nor is the direction of T uniformly opposite to that of QRS. Apart from these considerations there is no reason, theoretically, why the function of a bundle branch should

be impaired during a short period of an ectopic rhythm, while it can conduct impulses from the sinus at a faster rate. In both tracings (Fig. 8 and 9) lead II shows a ventricular complex intermediate between that of nodal and sinus beats when it is preceded by a P wave, with a P–R interval of 0·11 sec. The R–T interval is increased by up to 0·03 sec., but not more.

These appearances have some similarity to the short P–R, wide QRS pattern, which has been described in particular by Wolff, Parkinson, and White (1930) and by Hunter, Papp, and Parkinson (1940), except that there is no constant relation between the P wave and the ventricular complex and that a passive ectopic rhythm is obviously involved. Many theories have been advanced to explain these complexes, but in the present instances a centre near the A-V node with rhythmicity greater than that of the node itself and from which impulses reach the ventricles by an unusual pathway seems most acceptable. An abnormal conducting path seems indicated by the occurrence of complexes of intermediate form when preceded at sufficient interval by a P wave. These presumably represent a fusion beat the result of two impulses one from the ectopic focus the other from the sinus, conducted along their own separate routes. Whatever view is accepted, however, the important point is that complexes of this type should not be held to represent a myocardial defect.

Summary

Clinical and cardiographic findings are given of 8 cases showing conduction changes among a series of 83 patients with diphtheria. Of 4 with latent block, a prolonged P–R interval has persisted in one for five months. Bundle branch block in 4 un-immunized children, aged 12 or less, and all died; and complete block was recorded in one of these four. In 2 others bizarre ventricular complexes were found in association with a passive ectopic rhythm; at first sight these suggest a bundle branch lesion: but like the short P–R, wide QRS syndrome, which seems a related condition, these changes do not appear to have any prognostic significance.

I have to thank William McNaughtan for his kind help with the histology; and George Chesney and Gordon Smith, Medical Officers of Health, for kindly allowing me to investigate patients in infectious diseases hospitals.

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ELECTROCARDIOGRAPHIC CHANGES AND THE EFFECT OF NIACIN THERAPY IN PELLAGRA

BY

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In a previous communication (Rachmilewitz and Braun, 1944), we reported on electrocardiographic changes in patients showing clinical signs of niacin (nicotinic acid) deficiency, which were eliminated by administration of this vitamin: we concluded that they were due to this specific deficiency. Our observations on the effect of niacin on these cardiographic changes have since been extended, and the results of these studies are now reported.

Present Investigation

Clinical and cardiographic studies were made on 27 patients suffering from pellagra. The outstanding clinical manifestations were those attributable to niacin deficiency such as pellagrous dermatitis, stomatitis, gastro-intestinal disturbances (most frequently diarrhœa), and mental symptoms. In 22 cases there were typical skin lesions of pellagra, varying in degree and intensity; in some the acute erythematous lesions were present, in others there was hyperkeratosis and pigmentation of the exposed parts of the body. In 3 cases no skin changes were present; 3 other patients had had typical pellagra dermatitis on previous occasions, but not at the time when the studies were made. In these 6 cases the diagnosis of the deficiency state was based on glossitis and on gastro-intestinal and mental disturbances. In addition to the diagnostic features of niacin deficiency, some cases of the entire group also exhibited signs of ariboflavinosis, such as, cheilosis, angular stomatitis, and corneal vascularization. In 10 of the cases there was also evidence of thiamin (B_1) avitaminosis consisting of pain in the calf muscles, para-æsthesia, muscular weakness, and cramps, as well as objective findings indicating peripheral neuritis and sometimes also pyramidal involvement.

No one of the cases included in this report had obvious disturbances of the cardiac function and no one was suffering from heart failure as seen in beriberi heart. When œdema of the lower extremities was present it was associated with hypoproteinæmia, but was obviously not due to cardiac insufficiency. The subjective complaints of the patients referable to the heart were insignificant; only a few patients experienced a feeling of oppression and palpitation. Corresponding to the poor general condition of the patients and the state of malnutrition, the blood pressure on admission was usually below normal, and increased gradually with the clinical improvement. There were no striking deviations in the pulse pressure. The pulse rate, before the specific treatment, varied from 37 to 110, ranging in most from 60 to 80, and scarcely changed after the specific treatment. In the few cases with a rapid pulse, it became slower after treatment. In one case a bradycardia of 37 beats a minute disappeared with recovery.

Clinical and X-ray examinations showed the heart to be normal or sometimes subnormal in size. In a small number of cases circulation time and venous pressure estimations were made and normal values were observed.

Cardiographic tracings were taken before treatment and at frequent intervals following various therapeutic procedures, consisting of individual vitamins of the B complex. Since we were concerned particularly with the differentiation of the effect of niacin from that of thiamin, a number of the cases were put on a vitamin B_1 poor diet, while receiving niacin, while in others vitamin B_1 was given during a certain control period before the institution of niacin treatment.

Group 1. *Cases with Prompt Response to Niacin*

This group comprises 16 patients, all with cardiographic changes of varying degrees and intensity before treatment. The age of these patients ranged from 16 to 65, the majority being below 50. The most striking changes were frequently seen in the younger patients, but the response to treatment was equally effective in the older patients. The cardiographic changes were manifested mainly on the final deflection: alterations of the S–T segment or of the T wave were present in all those with abnormal records. S–T depression in at least two limb leads was present in 9 cases; in 4 S–T was below the isoelectric line in one lead only. Abnormalities of the T wave in at least two leads were present in the entire group of cases; the T waves were negative, absent, diphasic, or flattened. In all except three, chest leads (CF) were taken. Out of these 13 records with chest leads 10 showed negative or flat T waves. The ventricular complexes, the P waves, and the P–R intervals were practically normal in all the records.

In all cases the response to niacin treatment was an improvement of the cardiogram. The positive effect was usually seen after 4–5 days of treatment, which consisted of niacin by mouth in daily doses of 300 to 500 mg. Only occasionally, in patients suffering from severe diarrhœa or vomiting, the peroral administration was supplemented by intravenous injections of 50 to 100 mg. daily. In most cases the optimal effect was obtained after 3 to 5 days and remained so after discontinuation of the medication. In some cases, however, the treatment had to be continued because of incomplete improvement and in these a normal curve was obtained after continuing the treatment for another 10 to 14 days. The cardiographic and clinical improvement were not always parallel, and a normal pattern was frequently obtained when the dermatitis and the changes in the mouth and gastrointestinal tract were still present.

The pathological character of the cardiogram disappeared usually simultaneously in all leads and the improvement was most striking where the changes had been the most prominent. The S–T depression disappeared and the T waves became positive or more elevated.

Table I shows the changes that took place as the result of the treatment. The degree

TABLE I

Case No.	Sex and Age	Pulse on admission	Electrocardiographic findings	
			Before treatment	After treatment
1	F. 30	80	T I absent, T II, T III, T IV negative, depression of S–T (II, III)	T I, T II upright, T III, T IV absent, S–T (II, III) isoelectric
2	M. 50	37	T I absent, T II, T III diphasic, depression of S–T (II, III)	T I, T II, T III, T IV upright, normal, S–T (II, III) isoelectric
3	M. 65	66	Extrasystoles, T I absent, T II, T III slightly negative, depression of S–T (II, III)	Sinus rhythm, T I absent, T II, T III positive, S–T (II, III), isoelectric
4	F. 25	110	T II flat, T III absent, depression of S–T (I, II, III)	T II upright +, T III absent, S–T (II, III) isoelectric
5	F. 50	80	T I, T II flat, depression of S–T (I, II, III)	T I upright +, S–T (I, II, III) isoelectric
6	F. 51	80	T I flat, T IV negative, depression of S–T (I, II, IV)	T II upright ++, T III upright ++, T IV positive
7	M. 50	85	T I, T II, T III, T IV flat, depression of S–T (II)	T II upright ++, T III upright ++, T IV upright ++, S–T (II) isoelectric
8	F. 45	60	T I, T II flat, T III negative, T IV diphasic	T I upright +, T II upright ++, T III positive, T IV upright ++
9	M. 50	58	T I absent, T II, T III flat, depression of S–T (II)	T I positive, T II upright +, S–T (II) isoelectric
10	F. 45	80	T I flat, diphasic, T III negative, TII, T IV flat, depression of S–T (I, II)	T I upright +, T II upright ++, T III positive, T IV upright +, S–T (I, II) isoelectric
11	M. 58	62	T I, T II, T III, T IV flat, S–T (I) above zero level, S–T (II) depressed	T I upright +, T II upright ++, T IV upright ++, S–T (I, II) isoelectric
12	M. 20	80	T I flat, diphasic, T II flat, T III, T IV absent, depression of S–T (I, II)	T I, T II, T IV upright +, S–T (I, II) isoelectric
13	F. 30	52	T I, T II flat, diphasic, T IV negative	T I upright +, T II upright ++, T IV negative
14	M. 26	80	T I absent, T II, T III flat, depression of S–T (II, III)	T I flat, T II upright ++, T III upright ++
15	F. 60	58	T I, T II, T III flat, T IV negative, S–T (II, III) elevated	T I upright +, T II upright ++, T III upright +, T IV positive, diphasic, S–T (II, III) elevated
16	M. 16	85	T I, T II, T IV flat, T III negative, depression of S–T (I)	T I upright +, T II upright +, T III negative, T IV upright ++, S–T (I) isoelectric

of elevation of the T waves following niacin administration was designated as + corresponding to an elevation of 0·5 mm. ± 0·25 mm.; as ++ corresponding to an elevation of 1 mm. ± 0·25.; and as +++ corresponding to an elevation of 1·5 mm. ± 0·25 mm.

The following are a few typical case histories.

Case 6. A woman of 51 was first seen in the out-patient department 18 months before her admission to hospital. She then had pellagrous dermatitis for which niacin was prescribed. She discontinued treatment because of a burning sensation in the skin following the intake of the drug. During this time she complained of general weakness and poor appetite, and mental disturbances appeared—irritability, depression, and defects of memory. A fortnight before admission, she started a temperature which continued for 10 days and was accompanied by diarrhœa. Subsequently her mental condition deteriorated rapidly and for this reason she was admitted on 8/12/42.

On admission she was disorientated, restless and confused, and there was no control of fæces and urine. Slight pellagrous changes were seen on the back of both hands. The tongue, lips, and gums were bright red and sore. In addition, angular stomatitis as well as seborrhœic accumulations in the naso-labial folds were present. The reflexes of the upper and lower extremities were exaggerated and there was a right patellar clonus and positive Babinski and Oppenheim on the same side.

Laboratory findings. Urine and stools, normal. Blood picture: Hb. 12·5 g.; red blood cells 3,600,000; white blood cells 7,600 with a normal differential count. Blood chemistry: urea 31·5 mg., sugar 92 mg., NaCl 598 mg., total protein 5·74 g., albumin 4·30 g., each per 100 c.c. Pyruvic acid in the urine 174 mg. The examination of the gastric juice after a caffeine test-meal and histamine injection revealed complete achylia.

Physical examination of the heart showed normal findings; pulse rate 80, blood pressure 110/90. Fig. 1A, taken on Dec. 9, showed a depressed S–T interval in the first, second, and fourth leads and a negative T wave in the fourth lead. Treatment with niacin was started on Dec. 9; 500 mg. by mouth and 50 mg. intravenously were given daily. After three days a marked change in the patient's mental condition took place. She became coherent, orientated, and began to eat. Control of urine and fæces was also regained. Four days after the start of treatment Fig. 1B showed improvement; S–T II became less depressed, the T waves in the three limb leads became more elevated and a positive T wave appeared in the fourth lead. After continuous treatment with niacin the spastic state of the extremities gradually improved and the clonus disappeared.

Case 7. A 50 year old man, of poor social condition, was brought to the hospital on 5/11/42, in a state of mental stupor which, according to information obtained from relatives, was of 5 days'

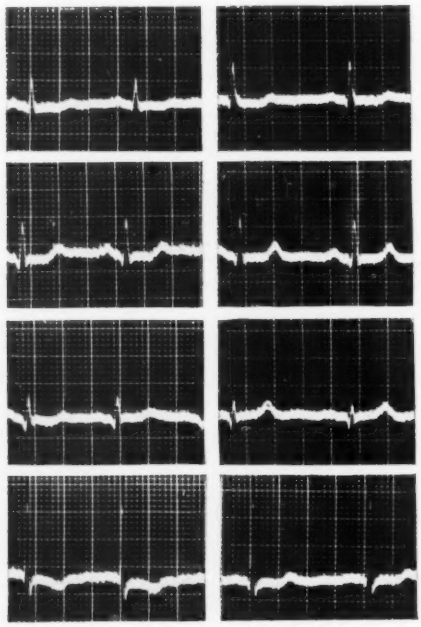


FIG. 1.—Case 6. (A) Before treatment. (B) After 4 days of niacin treatment.

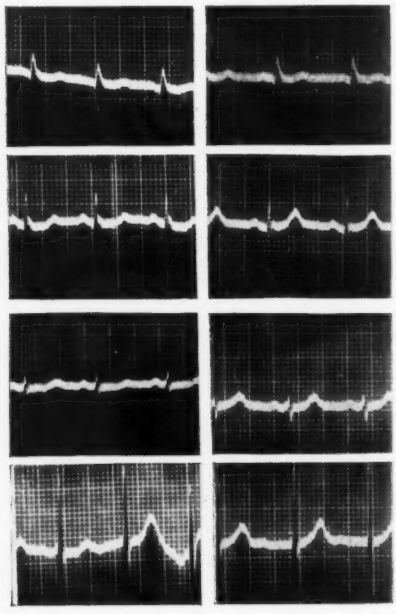


FIG. 2.—Case 7. (A) Before treatment. (B) After 5 days of niacin treatment.

duration. The acute illness was preceded by vomiting and severe diarrhœa persisting during 3 weeks. The patient, on admission, was incoherent, and there was no control of urine and fæces. There was marked emaciation and slight œdema of the lower extremities; no evidence of pellagra dermatitis was present, except for slight hyperkeratosis with pigmentation on the back of the feet and hands. The patient exhibited signs of stomatitis and cheilosis. The reflexes of the lower extremities were decreased.

Laboratory findings. Urine: trace of albumin, a number of pus cells in the sediment, and the culture positive for *Staph. aureus.* The stool contained ova of ascaris. Blood picture: Hb. 70 per cent; red blood cells 2,700,000; white blood cells 8,400 with a normal differential count. Blood urea 35 mg., NaCl 650 mg., sugar 86 mg., total protein 5·76 g., albumin 3·8 g., vitamin C 0·4 mg., each per 100 c.c. Pyruvic acid in the urine 153 mg.

The clinical examination revealed normal findings in the heart, which was not enlarged. Pulse rate 85, blood pressure 105/70. Fig. 2A, taken immediately after admission, and also 24 hours later after parenteral administration of 2 litres of physiological saline solution, showed S–T depression in the second lead and low positive T waves in all leads. From November 6 to 11, niacin was given, 500 mg. daily by mouth and 100 mg. intramuscularly. Two days after beginning of treatment the mental state began to clear up, the patient began to eat and regained control of urine and fæces. This improvement continued during the following days. Fig. 2B, taken November 11, showed S–T II isoelectric and marked elevation of T II, T III, and T IV.

Case 8. A 45 year old woman, with a history of chronic amœbiasis and repeated attacks of diarrhœa, especially during the hot summer months. The first appearance of pellagra dermatitis was noted three years ago. Since then, each attack of diarrhœa was followed by a burning sensation in the tongue and lips as well as by dermatitis on the back of both hands. On 22/7/43, the patient was admitted to hospital, presenting clinical symptoms of pellagra of two months' duration. There were digestive disturbances and psychic changes. The patient also complained of pain in the arms and legs, but no abnormal neurological findings were obtained. No œdema was noted.

Laboratory findings. The stool contained *Entamœba histolytica.* The gastric juice analysis showed complete absence of free hydrochloric acid following caffeine by mouth and histamine injection. The blood picture : Hb. 9·25; red blood cells 3,600,000. Blood chemistry: urea 21 mg., sugar 81 mg., ascorbic acid 0·6 mg., each per 100 c.c. Pyruvic acid in the urine 190 mg.

The clinical findings of the heart were essentially normal and there were no signs of heart failure; the pulse rate was 60 and the B.P. 115/70. A cardiogram, taken on July 24, showed low positive T waves in leads I and II, T III inverted and T IV diphasic. After three days of niacin medication consisting of daily doses of 350 mg., the clinical signs of deficiency began to clear up. A cardiogram, taken on July 27 showed marked elevation T I, T II, the negative T III became slightly positive; the most striking improvement, however, took place in T IV which became high and upright. The same pattern was obtained after continuing treatment with niacin for another week.

Group II. Cases with Delayed Response to Niacin

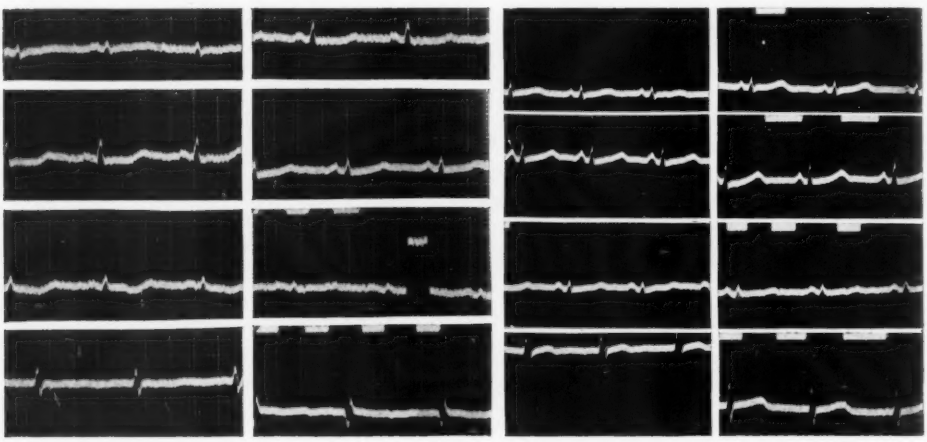
In this group, consisting of two patients suffering from severe deficiency of the vitamin B complex, the immediate improvement in the clinical symptoms and in the altered cardiogram following administration of niacin was slight or absent. In addition to the vitamin B deficiency these patients had also appreciable œdema of the lower extremities and ascites due to severe hypoproteinæmia and hypoalbuminæmia.

In the course of treatment the improved absorption and utilization of food in one case and plasma infusion in the second case resulted in a rise of the blood proteins and disappearance of the œdema. Niacin was again administered and was followed by a noticeable improvement of the cardiogram. These cases will be described briefly.

Case 17. A 40 year old woman suffering from repeated attacks of diarrhœa and chronic malnutrition was admitted on 10/12/43 in an extremely poor condition. She was highly emaciated and showed œdema of the lower extremities. The clinical symptoms of vitamin B deficiency were the following: mental deterioration with incontinence of urine and fæces; typical pellagrous dermatitis on the dorsum of both hands, atrophic glossitis, and severe diarrhœa; in addition there were neuritic manifestations, consisting of hyperreflexia and a positive Babinski reflex on the right side. Thus there was evidence of both niacin and thiamin deficiency. Laboratory examinations revealed a moderate degree of normocytic anæmia and marked hypoproteinæmia with hypoalbuminæia (total protein 4·7 g., albumin 1·93 g., each per 100 c.c.

The heart was normal in size with no evidence of failure. There was no pulmonary congestion and no hepatic engorgement. The pulse rate was 60, the blood pressure 105/65. Fig. 3A, taken on admission, December 10, showed marked abnormalities in all leads, low voltage of the QRS complexes, S–T II and S–T III noticeably depressed, T I and T IV absent, T II and T III low positive. During the following six days the patient was given a diet which contained only 0·5 mg. vitamin B_1; to this was added niacin 500 mg. by mouth and 100 mg. intramuscularly daily. This resulted in

some improvement of the dermatitis and the mental state. The diarrhœa, however, was hardly influenced. Fig. 4B, taken on December 16, showed slight improvement: a small T wave appeared in the first lead and the S–T depression in leads II and III disappeared. Niacin was then discontinued and for the following twelve days vitamin B_1 was given, 30 mg. daily intramuscularly. At the end of this period no improvement of the clinical condition was noted and the degree of the œdema remained the same. A cardiogram taken on December 28 was practically the same as before. The following fortnight, although no specific treatment was given, was characterized by gradual and steady clinical improvement of the patient and a marked increase in diuresis, which finally resulted in complete loss of the œdema. The subsidence of the diarrhœa and improved absorption of food resulted in an increase of the serum proteins to 6·5. Fig. 3C, taken on January 10, showed slight elevation of the T waves in all leads, the voltage of the QRS complex remaining the same. During the following six days niacin was given again, the daily medication consisting of 500 mg. by mouth



A B C D

FIG. 3.—Case 17. (A) Before treatment. (B) After 6 days of niacin treatment. (C) A fortnight later, after general improvement and increase in serum proteins. (D) After a second course of niacin treatment during 6 days.

and 100 mg. intramuscularly. Fig. 3D, on January 16, showed further improvement of the T waves in all four leads without changes in the voltage of the QRS complexes.

In this case, which was characterized by niacin and B_1 deficiency and by marked œdema due to hypoproteinæmia, the first trial with niacin produced only slight improvement of the cardiographic pattern; the administration of B_1 had no effect. With the gradual amelioration of the general condition of the patient together with better utilization of food, loss of the œdema, and rise in serum proteins there was a gradual improvement. At this last stage, a short course of niacin caused additional improvement of the cardiogram.

Similar observations were made in *Case* 18. This was a woman, 30 year old, who had been under treatment in hospital several times during the last three years because of severe pellagra precipitated by excerbations of chronic purulent sinusitis. On last admission, 13/7/43, the patient had fever and severe diarrhœa. The outstanding findings at this time were œdema of the lower extremities and ascites, severe atrophic glossitis, and mental changes. The heart was not enlarged on clinical and fluoroscopic examination; the contractions, however, were feeble. There was no distension of the cervical veins and the liver was not enlarged. The pulse rate was 65, B.P. 120/80. The stools contained cysts of *Entamœba histolytica*. The blood picture showed a moderate degree of hypochromic anæmia; blood proteins 3·7 g., albumin 1·3 g., per 100 c.c. Fig. 4A, 13/7/43, showed marked abnormalities especially of the final deflections of all leads. The first trial with niacin (7 days 500 mg. orally and 100 mg. intramuscularly), did not produce appreciable changes in the clinical state of the patient, the œdema rather increased during this period. Fig. 4B, taken on July 21, showed further deterioration, the T waves in the second and third leads becoming slightly negative.

Between July 21 and July 27, only vitamin B_1 was given, 40 mg. daily intramuscularly. This treatment had no effect on the œdema, the diarrhœa, or the cardiogram. On July 30, a plasma infusion of 400 c.c. was given. Since that date an increase in diuresis took place; this was accompanied by gradual but steady diminution of œdema and ascites. At the same time the diarrhœa markedly diminished in severity and the patient began to eat, the diet containing 70 g. animal protein per day. On August 7, the total proteins were 5·7 g. and the albumin 3·3 g. per 100 c.c. At this time, another tracing was taken which still showed severe pathological changes. The voltage of the

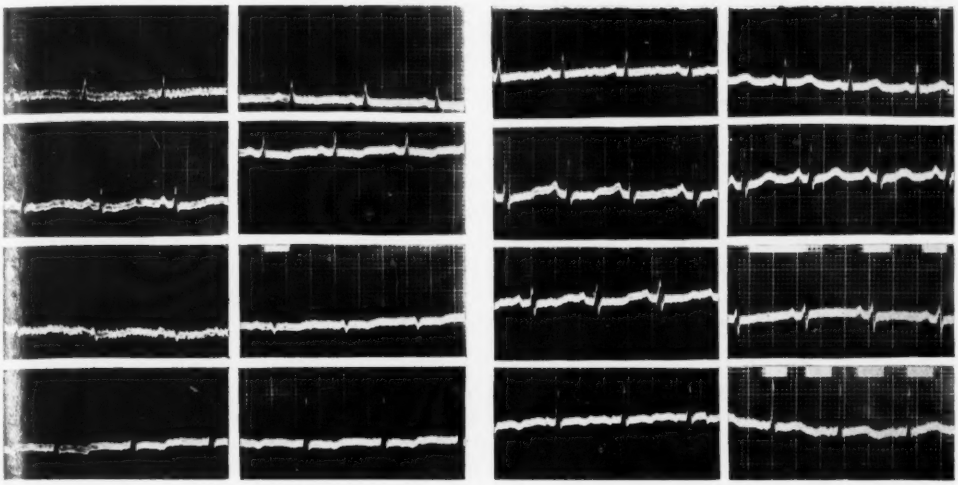


FIG. 4.—Case 18. (A) Before treatment. (B) After 7 days of niacin treatment (first trial). (C) After thiamin treatment and plasma infusion. (D) After 5 days of niacin treatment (second trial).

QRS complexes, however, increased (Fig. 4C). The last trial with niacin (5 days of 300 mg. by mouth daily) was followed by striking improvement of the cardiogram, which became practically normal (Fig. 4D).

Group III. Cases of Pellagra with no Alterations of the Electrocardiogram

In the third group comprising 9 cases, the original cardiographic changes were very slight or entirely absent, although the age incidence in this group was even higher than in the first group. Analysing the clinical symptomatology of these patients, it became evident that the outstanding sign was the pellagrous dermatitis, the visceral deficiency manifestations being either very slight or entirely absent. All these patients were ambulatory and visited the out-patient department because of the skin changes. Some of them complained of burning sensation in the tongue and lips. It seems thus that the heart in pellagra is affected mainly in cases in which other visceral organs, such as the brain, stomach, and intestines, show clinical evidence of involvement. When skin changes alone are present in pellagra alterations in the cardiogram may not occur.

COMMENT

The only vitamin deficiency known to be associated with cardiovascular disturbances is that of vitamin B_1, e.g. beriberi heart disease which is manifested by cardiac enlargement and heart failure. Experimental as well as clinical B_1 avitaminosis is associated with cardiographic changes which disappear following B_1 administration. The electrocardiogram was also found frequently changed in pellagra. Since in deficiency diseases in man several factors of the vitamin B complex may be lacking simultaneously, the presence of cardiographic changes in pellagra was attributed to B_1. Feil (1936) in a study of 38 cases of pellagra found 19 with abnormal cardiograms, chiefly concerning the final deflection of the ventricular complex; in some instances, they returned to normal with recovery. The conclusion drawn by this author was that pellagra and beriberi apparently affect the heart physiologically in much the same way. Porter and Higginbotham (1937), on the other hand, found no characteristic changes in endemic pellagra and concluded that beriberi and pellagra have no comparable effect on the heart.

The above-mentioned observations were made before the introduction of niacin in the treatment of pellagra.

Mainzer and Krause (1940), found a high incidence of abnormal cardiograms in pellagrins in Egypt, but believed that these changes were not characteristic of pellagra and that their occurrence was not sufficient to warrant the conclusion that they were caused by a deficiency of niacin. However, they noticed that there was a parallelism between the course of the disease and the cardiographic changes, and that these disappeared rapidly in some cases following niacin therapy. In the first case report of pellagra successfully treated with niacin, Smith, Ruffin, and Smith, (1937) found low upright T waves in all leads; on the seventh day of treatment the T waves had returned to normal.

The cardiac manifestations in pellagra obviously differ from those in beriberi. Observations reported by others as well as by ourselves clearly show that the heart in pellagra is not enlarged; its size is normal or frequently subnormal. Obvious disturbances of cardiac function and heart failure have not been found in pellagra as is the case in beriberi heart. In our cases of pellagra with œdema of the lower extremities and ascites there was no evidence of congestive heart failure, the œdema being explained by marked hypoproteinæmia. Vitamin B_1 had no effect on diuresis in these cases; only the rise in serum proteins was accompanied by an increase of diuresis and disappearance of the œdema.

It remained, however, to be shown that the cardiographic changes in pellagra are not due to deficiency of vitamin B_1. During recent years it has become possible by therapeutic tests with pure vitamins to separate the various symptoms and signs of most of the specific avitaminoses constituting the syndrome of pellagra. In order to eliminate the action of B_1, some of our cases were put on a vitamin B_1 poor diet while receiving niacin. In other cases vitamin B_1 was given first to establish whether this vitamin had any effect on the clinical condition and on the cardiographic changes. It was thus found that only the administration of niacin resulted in most cases in prompt and striking improvement of the clinical symptoms as well as of the cardiographic changes, showing that these changes in pellagra are due specifically to niacin deficiency.

Our observations seem also to indicate that there is a parallelism between the cardiographic abnormalities and the visceral manifestations of the disease. The most striking changes were seen in patients having lesions in the mouth and mental and gastro-intestinal disturbances, sometimes in the absence of dermatitis. On the other hand, the presence of skin lesions alone in chronic pellagrins without obvious involvement of the visceral organs may be associated with normal cardiograms.

The lack of immediate response to niacin in the two cases in which pellagra was associated with severe hypoproteinæmia is of special interest. In these cases the administration of niacin at first had no effect, either on the clinical signs of pellagra or on the cardiographic changes. A positive effect on both was seen only after restoration of the blood proteins. This lack of response to the specific treatment, as long as hypoproteinæmia existed, suggests that in these cases the hypoproteinæmia interfered with the utilization of niacin. Evidence of an interrelationship between protein intake and niacin utilization was given in the experiments of Sarett *et al.* (1942), who showed that in dogs there was an inverse relationship between protein intake and niacin excretion. The state of the liver in hypoproteinæmia might be responsible for the lack of utilization of niacin. Evidence of liver damage due to protein depletion in dogs was given by Elman and Heifetz (1941), who showed that the liver cells in these animals become vacuolated and that nearly all of the stainable cytoplasm becomes transparent. It may be assumed that in our cases disturbances of liver function during the state of hypoproteinæmia and hypoalbuminæmia were responsible for the failure of response to niacin. That liver damage actually existed was proved in one of these cases by means of the hippuric acid test. There was at the beginning no excretion of hippuric acid after intravenous administration of 2·0 g. of sodium benzoate. With the restoration of proteins, the excretion rose gradually to 0·65 g., which is practically normal.

The cardiographic abnormalities in pellagra, consisting mainly in alteration of the final deflection of the ventricular complex, are in themselves not specific and their presence does not necessarily indicate pellagra as the cause. Similar changes may occur in beriberi and in organic heart disease, most frequently in arteriosclerotic coronary artery disease. Only the fact that in pellagra these changes are reversible and disappear or improve after niacin admin-

istration, proves conclusively that they are caused by niacin deficiency and hence are a part of the pellagra syndrome.

The question naturally arose whether treatment with niacin has a similar effect on the cardiographic changes accompanying organic heart disease; particularly since observations were reported recently that niacin had a beneficial effect on pain in angina pectoris (Neuwahl 1942). In order to clarify this question six patients suffering from arteriosclerotic heart disease were selected. These patients showed depression of the S–T segment and flattening or inversion of the T wave in at least two limb leads. There was no history of recent cardiac events to account for these changes. These patients were given niacin for a period of 8 to 10 days and this medication had no effect whatsoever on the cardiograms.

The changes seen in pellagra can also resemble those present in myxœdema, namely flattening or absence of the T waves, and lowering of the voltage of the ventricular complexes. Even the heart rate in pellagra may occasionally be as low as in myxœdema. The myxœdema heart and the abnormal curves in this disease are known to be specifically affected by the administration of thyroid extract. There was, however, a possibility that niacin might also improve the pattern in myxœdema by influencing the metabolism of the heart muscle or by improving the circulation in the heart. Three cases of myxœdema with low basal metabolic rates and characteristic cardiographic changes were given niacin during 6 to 8 days before thyroid treatment. In all these cases niacin in the usual doses had no effect on the curves, which became normal only after thyroid medication.

The specific action of niacin on the cardiogram in pellagra could be explained in the first place by its effect on the coronary circulation. Niacin is known to produce vasodilatation of the skin as indicated by increased temperature and flushing in various parts of the body after administration of the drug. It is doubtful, however, whether the blood vessels of the visceral organs are at all affected by niacin. Investigations (Lomann *et al.*, 1941) have shown that the blood flow through the brain is hardly increased by this substance, although the pial vessels were found to be dilated (Moore, 1940). Furthermore, the vasodilatory action of niacin is transient in character; flushing of the skin usually disappeared within half an hour. According to the studies of Bean and Spies (1940) and our own observations, niacin has no immediate effect on the cardiogram. In several of our cases of pellagra cardiograms were taken before and immediately after the intravenous administration of 50 mg. of niacin and no reversal of the pathological changes was noted. The mode of action of niacin on the heart can hardly therefore be sought in its vasodilatatory effect on the coronary vessels. It seems more likely that the influence of niacin on the electrocardiographic changes in pellagra is due to some more fundamental action.

Cardiographic changes due to niacin deficiency are mainly manifested by alterations of the S–T segment and the T wave. Inasmuch as metabolic changes in the heart muscle are reflected in the T wave (anoxemia, thyroid deficiency, and avitaminosis B_1), any factor affecting the metabolism of the heart muscle may also affect the character of the T wave. According to McLeod (1938), the prolongation of the recovery period of cardiac muscle with a delay in the oxydation of the products of metabolism, is one of the factors responsible for the lowering of the T wave. It is suggested, that the changes in the T waves produced by niacin deficiency may also be of metabolic origin. Niacin is the chemically active fraction of the coenzymes which are essential for the intermediate metabolism of carbohydrates. Axelrod, Spies, and Elvehjem (1941) found a marked diminution of coenzyme I in the striated muscle of human subjects, deficient in niacin, and assumed that the coenzyme content may affect the ability of the human muscle to carry out its oxidative function. It seems logical, therefore, that the coenzyme deficiency also results in an altered metabolic state of the heart muscle. This view is further supported by the fact that the changes are reversible, i.e. they disappear after the administration of niacin.

Summary

The effect of niacin therapy on the cardiographic changes in 27 patients suffering from pellagra was studied. In 16 of them, with pronounced visceral manifestations of the disease, the response to niacin was prompt; the cardiogram improved or returned to normal after

several days of treatment. In some cases thiamin was given without any effect; these cases responded promptly to subsequent niacin treatment. In two cases complicated by severe hypoproteinæmia, the response to the first trial with niacin was slight or absent. Only after restoration of blood proteins was the effect of niacin on the cardiographic changes observed. In 9 cases which only had skin lesions no cardiographic abnormalities were found and no changes followed treatment.

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BLOOD VOLUME DETERMINATIONS WITH RADIOACTIVE PHOSPHORUS

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In experiments on animals, Smith, Arnold, and Whipple (1921) compared the three then known methods for determining the circulating blood volume, namely, the Welcher method, the carbonic oxide method, and the dye method. They recommended the method worked out by Dawson, Evans, and Whipple (1920), the so-called " blue azo dye T 1824 " method, for determinations of plasma volume. Gibson and Evans (1937) modified this method and with their co-workers applied it to a comprehensive series of clinical problems. There is no doubt that, thanks to these activities, plasma volume determinations have been aided by valuable experiences, but for studies of the circulating blood volume every method used, even the last-mentioned, lacks to a certain extent the prerequisites needed for completely reliable values. For example, when determinations of the plasma volumes are made by the " blue azo dye " method, the dye substance introduced is not taken up solely by the circulating blood but, as Gibson himself admits, is also taken up by, *inter alia*, the reticulo-endothelial system. Cardozo (1940), who made a special study of the passing of T 1824 into the lymphatic system in dogs, comes to the following conclusion: " The passing of the dye to the lymph interferes with a correct interpretation of a disappearance curve according to Gibson and Evans, and it usually results in the calculation of too large plasma volumes." Between 15 to 30 minutes after the injection of the dye substance into the blood stream the lymph assumed a blue colour and after two hours reached a concentration up to 49 per cent of that in the plasma.

It has been shown in previous works (Nylin, 1944 and 1945), by employing the method of Hahn and Hevesy (1940 and 1942) for labelling the red blood corpuscles with radioactive phosphorus, that in normal cases mixing and equilibrium between the injected labelled blood corpuslces and the blood stream are attained remarkably early—a contrast to the dye method. Gibson showed that " mixing time " does not set in until after 15 minutes in the special case, and on an average after 7·5 minutes for 15 normal subjects. The continuation of the curve Gibson calls the " disappearance slope," and he states that only relative constancy is attained in that the curve in its further course falls slowly towards the abscissa. It seems as though Hevesy's method affords the possibility of studying a number of circulation problems that had not been possible previously, because the fundamental prerequisite appears to have been satisfied, when it is possible to inject the subject's own blood corpuscles labelled with P^{32} which are continuously confined to the circulating blood for a relatively long time, and whose activity comes into equilibrium with the circulating blood remarkably early. Hevesy, Warburg, *et al.* (1944) made determinations of the circulating blood volume in normals both by Hevesy's and Hahn's methods with radioactive phosphorus and by the CO method and also by the dye method. As was expected, with the labelled blood corpuscles they obtained lower and, very probably, more reliable values than by the other methods.

In the present work Hevesy's method has been employed on clinical cases, it being of importance by means of fractioned specimens, preferably from arterial blood, to obtain a knowledge of " the dilution curve," and particularly in determinations of the amount of blood in dilated hearts, where the amount of residual blood has proved to have a great influence on the type of curve (Nylin, 1945). Not until one knows the course of the individual dilution curve can one indicate more closely where mixing and equilibrium take place and subsequently select the points, preferably the mean value of several specimens, which are to be the basis for the calculation of the circulating blood volume.

Methods and Results

In the present work the same method has been employed as in those previously published by the writer. For determinations of the circulating blood volume the activity was established, by means

of a Geiger counter, for the injected labelled blood corpuscles, and then for the fractioned specimens taken from the arterial blood. The calculation of the amount of circulating red blood corpuscles was made with the formula $x = A \times B$, where x indicates the amount of circulating blood corpuscles required in c.c., A, the amount of labelled blood corpuscles injected, and B, the relation between the specific activity of the labelled blood corpuscles injected and the specific activity of the blood specimens taken. The specific activity of the latter constitutes the mean value for a series of specimens after equilibrium had been attained, each value including 3–18 separate determinations in a single case. With the guidance of the hematocrit and the amount of blood corpuscles, the amount of plasma was calculated. Finally, the total of the amounts of plasma and blood corpuscles gives the circulating blood volume. In calculating the amount of blood corpuscles expressed in grams a specific gravity of 1·08, as used by Hevesy, has been taken.

The material comprises six subjects with normal hearts, six heart cases with varying ætiologies, and one case of anæmia; all were without signs of failure and had normal venous pressures. In addition there are two cases of typical cardiac failure, Case 14 with mitral stenosis and Case 15 with cardiosclerosis. The former had a venous pressure of 29 cm., the latter one of 17 cm. Both had much dilated hearts, as appears from their large heart volumes (see Table I).

For most cases detailed dilution curves have been published in an earlier work (Nylin, 1945). Among the normal cases, equilibrium between the injected activity and the circulating blood is attained already in the first minute in Case 1, and in the second and third minutes in the others. Case 2 was not subjected to a closer analysis of the dilution, but the specimens were taken as late as after the fifteenth minute. As emerges from Table I, the mean value for the amount of blood corpuscles for these seven normal cases is 1850 c.c., or 1998 g. per kilogram of body weight: these normal cases have a weight of circulating blood corpuscles of 33·4 g., somewhat less than that found by Hevesy *et al.*, which was 36 g. Nevertheless, the present material is so small that in this respect a comparison can hardly be made, but in each case the determination of the circulating blood volume is based, firstly, on a knowledge of the dilution curve in that individual case, and thus on a knowledge of when equilibrium was attained, and secondly on the mean value of a number of determinations on the same case.

In the group of compensated heart cases there is only one (Case 7), where equilibrium appears to be attained strikingly soon, in spite of the fact that the amount of residual blood in the heart would seem to be considerable. The heart volume is no less than 820 c.c./m.^{2} Repeated determinations with both decholin and with corpuscles labelled with radioactive phosphorus on the same patient showed remarkably short circulation times, which in this exceptional case could not be fully explained, though the possibility of a septal defect is not excluded. In the other cases in the last-mentioned group equilibrium set in later than in the normal cases, as appears from Table I; this conforms with the course of the dilution curve and the large heart volumes, which has also been pointed out in an earlier work (Nylin, 1945).

The circulating blood corpuscle volume in compensated heart cases, expressed in c.c., grams, or grams per kilogram of body weight, and the total amount of circulating blood do not diverge from the normal value but exhibit striking agreement with them. In these heart cases, too, the blood volumes given for the individual case are the mean values of a number of observations.

Of particular interest is Case 8, with a very large heart, 1230 c.c./m^2, where equilibrium appears to have been attained ten minutes after the injection of the labelled blood corpuscles. Four observations, made between 10 and 15 minutes after the injection, give a mean value of the amount of circulating blood corpuscles of 1275 c.c. The mean value of 8 observations 15–22 minutes after the injection is 1368 c.c. At the later determination an increase of 7·3 per cent in the circulating blood volume was obtained; that was probably due to the error of the method, which according to Hevesy *et al.* probably amounts to about 5 per cent. It is not out of the question that to some extent the increase may be due to the fact that as late as after the twenty-second minute, the activity had decreased somewhat and thus a somewhat too high figure for the amount of circulating blood corpuscles was indicated. We do not yet know with certainty how long the activity in the circulating blood remains constant.

The two with heart failure (Cases 14 and 15) have been subjected to detailed studies, and their dilution curves were published (Nylin, 1945). In spite of the considerable dilatation of the heart, probably with large amounts of residual blood, equilibrium nevertheless appears relatively early—from the second to the third minute. The amount of circulating blood corpuscles in Case 14 is as high as 46 g. per kilogram, and in Case 15 is 36 g. The total blood volume approaches twice the normal in Case 14, amounting to 6616 c.c. or 114 c.c. per kilogram of body weight. Remarkably enough Case 15 has neither so large an amount of blood corpuscles nor so great total blood volume in spite of a pronounced insufficiency on May 15, 1944. Ten days later, when all the symptoms of failure had receded, the œdema disappeared, and the body weight decreased by 12 kg., both the

TABLE I

CIRCULATING BLOOD VOLUME IN NORMAL AND CARDIAC CASES

Case No.	Diagnosis	Date	Weight Kg.	Heart volume		Venous pressure cm.	Circul. time (decholin) sec.	Hb.	Red cells	Hematocrit	Injected labelled corpuscles g.	Specific activity of injected corpuscles (10^6 omitted)	Mean specific activity of samples	Red corpuscles			Plasma volume ml.	Total blood volume		Time for samples after injection (minutes)	Number of samples
				c.c.	c.c./m²									c.c.	g.	g./kg.		c.c.	ml./kg.		
1	Normal	2/7/43	65	520	310	12	10–17–22	91	4·9	45	1·23	0·233	120	2213	2390	36·8	2705	4918	75·5	1–1·5	10
2	,,	8/11/43	47				?	64	4·4	38	1·07	0·179	107	1657	1789	38·0	2714	4371	93	15–20	7
3	,,	28/1/44	69				?			48	1·36	0·373	245	1919	2073	30·0	2079	3998	57·9	3–8	4
4	,,	8/2/44	75	978	501	12	17–27–42	88	5·0	45	1·23	0·1435	85	1922	2076	27·7	2346	4268	56·9	3–15	15
5	,,	28/2/44	63	575	340	9	9–19–24	78	4·4	40	1·10	0·196	148	1352	1460	23·2	2028	3380	53·7	2–9	16
6	,,	19/4/44	49				?	75	4·0	39	1·13	0·388	200	2037	2200	44·8	3056	5093	103·9	3–10	12
	Mean									42·5				1850	1998	33·4	2488	4338	73·5		
	Compensated heart cases																				
7	Aortic regurgitation?	25/5/43	72	1460	820	14	17–27–30	76	4·9	46	1·26	0·2297	14	1920	2074	28·8	2253	4173	58·0	0·5–1	18
8	Aortic regurgitation	30/3/44	46	1720	1230	10	17–30–56	68	4·2	40	0·87	0·093	59	1275	1377	30·0	1913	3188	69·3	10–15	4
	,, ,,	,,									,,	,,	55	(1368)	(1477)	(32·1)	(2052)	(3420)	(74·4)	15–22	8
9	Hypertension	16/3/44	67	2100	1200	13	37–67–85	90	4·7	43	1·20	0·135	70	2140	2311	34·5	2830	4970	74·2	5–10	3
10	Cardiosclerosis	29/6/43	52	1480	830	5	32–57–83	92	5·0	54	1·55	0·229	162	2037	2200	42·3	1735	3772	72·5	2–4·5	8
11	Constrictio cordis op.	12/6/44	65	821	470	10	13–20–29	76	4·5	41	1·23	0·095	59	1836	1983	30·6	2535	4371	67·2	5–19	8
12	Acute polyarthritis and endocarditis.	19/4/44	84	1005	480	?	?	72	4·3	38·5	0·97	0·229	102	2020	2182	26·0	3160	5180	61·7	3–5	5
13	Anæmia	22/3/44	48					64	3·0	35	0·97	0·314	211	1339	1446	30·1	2487	3826	79·7	3–6	4
	Mean									42·5				1795	1939	31·8	2416	4211	71·8		
	Decompensated heart cases																				
14	Mitral stenosis	23/8/43	58	2038	1235	29	60–85–95	67	4·2	38	1·07	0·645	257	2481	2680	46·2	4135	6616	114·0	2–5	10
15	Cardiosclerosis	15/5/44	62	1613	895	17	35–52–65	78	4·1	46	1·26	0·0918	52	2064	2230	36·0	2423	4487	72·4	3–13	8
	After treatment compared.	25/5/44	50	1352	845	5	20–37–47	96	5·1	52	1·46	0·11	88	1687	1822	36·4	1557	3244	64·9	3–11	5

amount of blood corpuscles and the total blood volume had decreased, the latter by no less than 28 per cent, naturally owing to the disappearance of the fluid. It is remarkable on the other hand that the amount of blood corpuscles decreased by no less than 18 per cent—perhaps to accumulate in certain depots—in spite of the fact that both the hæmoglobin and the number of red blood corpuscles increased considerably.

Summary

By the application of a new method worked out by Hevesy and his co-workers, employing blood corpuscles labelled with radioactive phosphorus, the circulating blood volume has been determined on both normal and cardiac cases, with and without failure. A prerequisate for the determination of the circulating blood volume is that the dilution curves can be established and thereby the time when equilibrium appears.

In this work the results in each case are based on the mean values of a number of determinations. The mean value for the amount of the circulating blood corpuscles in normal cases was found to be 1850 c.c., 1998 g. or 33·4 g. per kilogram of body weight. The mean value for the compensated cases is in agreement with the normal values at 1795 c.c., 1939 g. and 31·8 g. per kilogram of body weight. The total blood volume in the normal cases is 73·5 c.c. per kilogram of body weight, and in the compensated cases 71·8 c.c. Two cases of heart failure—and particularly one of them—show a considerable increase in both the amount of blood corpuscles and the circulating blood volume. The other case has been followed with repeated determinations after all signs of failure had disappeared, a great decrease in the circulating blood volume of no less than 28 per cent taking place simultaneously with the appearance of the interesting phenomenon that the amount of red blood corpuscles also decreased by 18 per cent.

I proffer my grateful thanks to Professor G. von Hevesy for all his kind advice, and I am greatly indebted to Professor M. Siegbahn for supplies of radioactive phosphorus.

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SINUS BRADYCARDIA WITH CARDIAC ASYSTOLE

BY

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The case history of a patient suffering from attacks of cardiac asystole with syncope is described. On superficial examination the condition appeared to be one of Stokes-Adams disease; electrocardiographic tracings, however, showed that there was no delay or block in the conducting system of the heart, but a persistent sinus bradycardia (about 24 beats a minute) interrupted by complete asystole for periods of at least 22 seconds. No report of a similar case has been found. The effect of exercise and various drugs upon the heart rate is described and the underlying basis of the condition discussed.

The patient was a woman of fifty-two years. She had led an active life until the onset of the present symptoms. Apart from excessive menstrual loss for nine years after the birth of her child, she had no history of previous illness. The menopause took place a year before admission.

In February 1943 she first complained of occasional dizziness, particularly after stooping. At this time she was found to have a regular pulse rate of 24 beats a minute. These attacks became rather worse two months before she was first seen in December 1943. During this month while in her garden she had her first attack of loss of consciousness. She felt faint and fell to the ground before she was able to sit down. Three weeks later she lost consciousness for the second time just after a cardiogram had been taken. Following this she had two or three attacks weekly until her admission to hospital on 29/1/44.

At this time her pulse was forceful and regular at 24 beats to the minute. The heart sounds were normal, the blood pressure somewhat raised (195/105). Radiographic examination of the heart showed slight generalized enlargement. There was no evidence of arteriosclerosis.

Shortly after admission it was observed that her pulse was not always regular; additional beats were often present, sometimes occurring singly and sometimes in short runs of two or three. She felt faint frequently and was aware that her heart had ceased to beat or was beating irregularly. At times she lost consciousness: sometimes this happened without her knowledge, for example, on several occasions she realized that she had fainted only because the cup she had been holding had fallen from her hand; usually she was distressingly aware of imminent loss of consciousness. Her description of her sensations at these times was as follows: "In very mild attacks there is a feeling of dizziness causing me to stand still if I am walking and a feeling as if my body was leaving me." In more severe attacks " there is a feeling as if cotton wool was being rammed into my arms and as if my arms and legs were in clamps." During these attacks she felt very frightened.

Observation of these attacks, which were now occurring very frequently, confirmed the absence of pulse at the wrist during them, and on auscultation no heart sounds could be detected. The pause, which might last for from 5 to 22 seconds, was usually followed by several rapid, irregular beats before the normal rate of 24 beats a minute was resumed. Tracings during these attacks showed that there was complete standstill of the heart followed by an increased rate, partly due to extrasystoles. During the attack the patient's face became pale and then flushed as the pulse returned, so that even minor attacks could easily be recognized by observation from the end of the bed. In more prolonged periods of asystole consciousness was lost. In these, after the preliminary pallor, a look of fearful expectation would appear, followed by movement of the head and eyes to the right with clenching and sometimes grinding of the teeth and swallowing movements; at times she would take a sighing inspiration, the arms being flexed at the elbows and the hands raised in a series of jactitating contractions of the forearms and clutching movements of the hands. It was difficult to tell at what stage consciousness was lost, but on several occasions the patient continued to talk for at least seven

seconds after the pulse had become impalpable, before she stammered and ceased speaking. On three occasions standstill was observed to last for 22 seconds. After long pauses the cardiac contractions were especially vigorous and the head and shoulders were shaken by each pulsation which could be clearly seen in the carotid vessels. At the same time a deep flush spread over her face.

The patient thought that the attacks were worse after effort and particularly noticed that the use of a bed-pan or even talking in an animated way precipitated them. The frequency with which they occurred when she was being examined suggested the possibility of an emotional precipitating factor. Air raids, including the dropping of heavy bombs in the vicinity, had no effect except on one occasion. The patient was then aware that her heart had suddenly started to beat more rapidly, and the night nurse reported that the rate rose to 100 beats a minute and continued at this level for ten minutes but then returned to 20 beats a minute; this was the only occasion at rest under natural conditions when a rate greater than 30 beats a minute was recorded. Although she usually slept well at night, irregular beats and long pauses were noticed during sleep by the night nurse.

At times she would have a series of attacks, being scarcely out of one before the next took place, over a period of several hours. Sometimes she vomited during these bad periods. On 27/2/44 she was examined while having a series of attacks following a good night. The first occurred while the patient was on the bed-pan. When seen later the pulse was irregular, with periods of standstill up to 10 seconds followed by irregular and often coupled beats. The face was flushed and became pale repeatedly. The patient vomited several times. On 12/3/44 she was observed for forty-five minutes during which at least fifteen attacks occurred and on one occasion three periods of asystole lasting from 7 to 9 seconds took place in one minute, the first with loss of consciousness. During the last three months of her stay in hospital the attacks became much less frequent and usually followed exertion.

After her discharge from hospital in August 1944, she continued to have frequent faint turns and lost consciousness several times weekly. At this time she was staying with friends away from home and was worrying about her husband and daughter. For three weeks before she returned home at the end of October she had no loss of consciousness, although she was aware of short pauses, double beats, and runs of four or five irregular beats. On 29/10/44 when she was examined her pulse rate was in the region of 20 and periods of coupling were frequent when only alternate beats got through to the wrist. On this day the blood pressure when first taken was 230/110, but after an hour the systolic pressure had fallen to 180 mm. The Wassermann reaction was negative. The blood sugar during a series of attacks was within normal limits. The serum potassium was 21·6 mg. per 100 c.c.

Electrocardiographic tracings were taken on a number of occasions. These showed that the basic rate varied between 18 and 24. The complexes showed normal sinus rhythm. There was constantly a large T wave, particularly in the second lead. Periods of cardiac standstill were observed up to 9 seconds and were followed by a rise in rate to 50 or more for a few seconds. Exercise had a similar effect. Impulses frequently occurred in pairs from the S-A node, but on other occasions the coupling was shown to be due to auricular or ventricular extrasystoles. Isolated auricular and ventricular extrasystoles were often observed. There

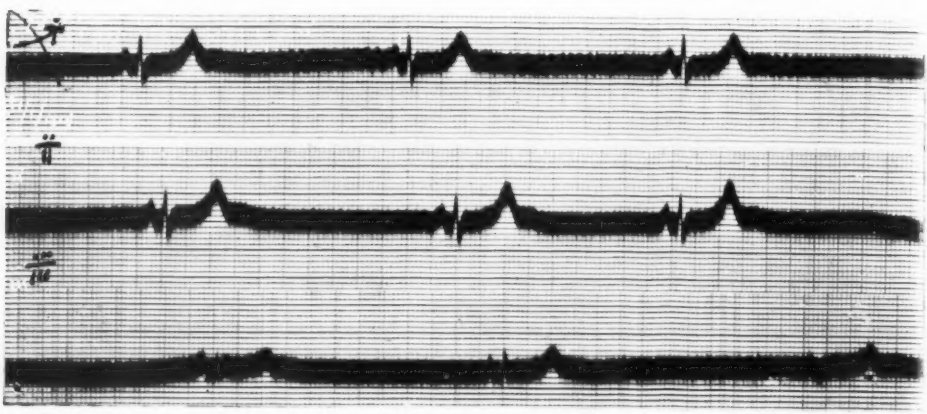

FIG. 1.—Electrocardiogram showing her usual basic rate of 24 a minute. All figures have been slightly reduced in size (43/50).

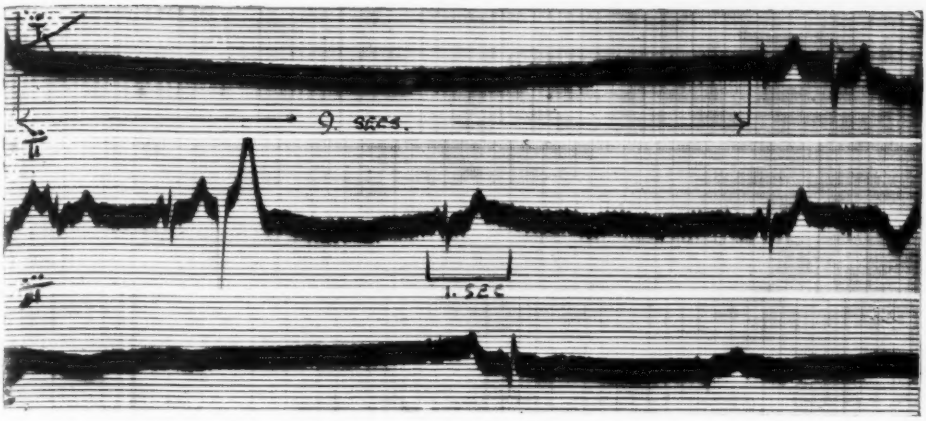

FIG. 2.—Asystole for 9 seconds in lead I. Lead II shows a ventricular extrasystole; lead III shows the end of a further period of asystole.

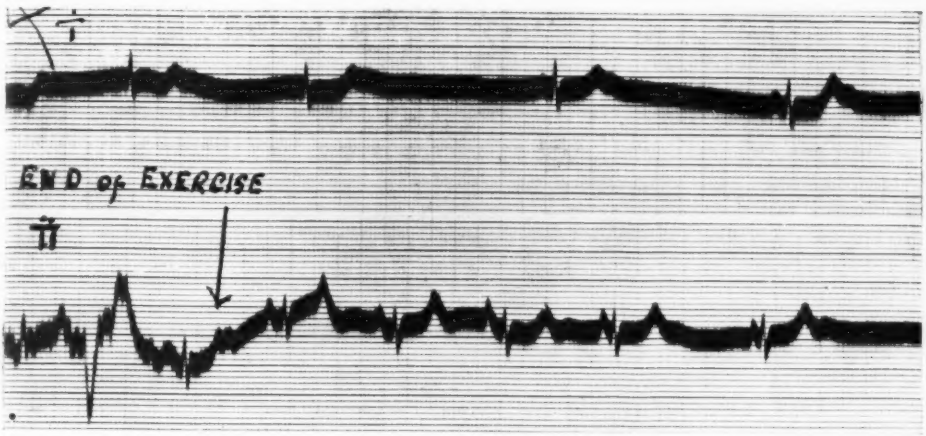

FIG. 3.—The increase of rate caused by exercise is shown in lead II.

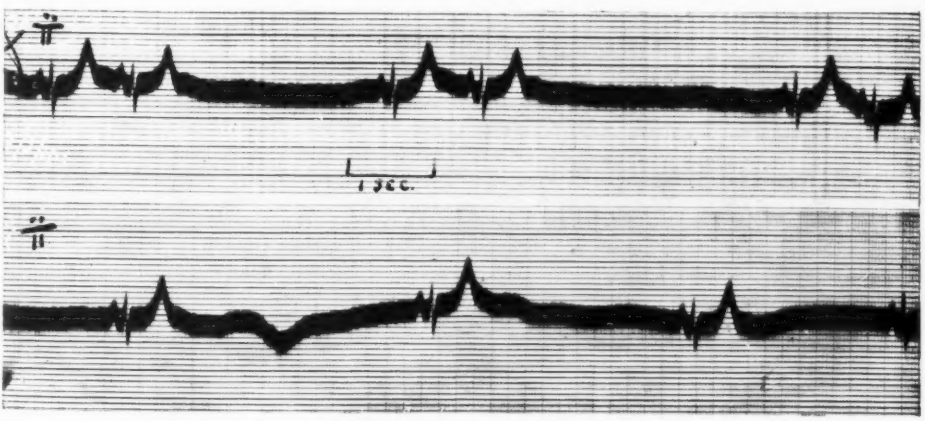

FIG. 4.—Coupled beats, the second being a premature beat arising from the sinus.

was no delay in conduction and no evidence of nodal escape or of ventricular rhythm during periods when the sinus failed.

On 22/6/44 a cardiographic tracing was recorded continuously for about half an hour, with a simultaneous electro-encephalogram. During this period every abnormality seen in previous cardiographic tracings was recorded. At times a regular rate between 18 and 24 beats each minute was observed. Premature beats giving rise to coupling at regular intervals sometimes occurred on from five to ten successive occasions, the extrasystole sometimes arising repeatedly from the ventricle, sometimes from the sinus or the auricle, and sometimes from varying sites after successive normal beats. On one occasion a period of asystole up to 12 seconds was followed by 15 ventricular extrasystoles in 11 seconds, on another 14 beats arising sometimes from the auricle and sometimes the ventricle were recorded in 10 seconds. Periods of asystole occurred frequently: on two occasions these lasted for 13 seconds, and once for 12 seconds. Asystole of 10–11 seconds occurred twice, 8–9 seconds three times, 7–8 seconds ten times, 6–7 seconds twelve times, 5–6 seconds thirteen times, and 4–5 seconds ten times. Such periods of asystole were followed by single normal beats, coupled beats, short runs of extrasystoles, or irregularly spaced beats with occasional ventricular extrasystoles.

The following example shows the extreme variations that could occur consecutively in 43 seconds—asystole for 7 seconds, a coupled beat, both impulses arising from the S-A node, an interval of 2·5 seconds followed by a normal beat and a ventricular extrasystole, an interval of 3 seconds, a normal beat followed by a premature auricular beat, asystole for 5 seconds, a normal beat followed by two ventricular extrasystoles in close succession, asystole for 5 seconds, a normal beat with a premature ventricular beat, asystole for 5 seconds, a coupled beat, both impulses arising from the S-A node, asystole for 4 seconds followed by another coupled beat from the S-A node, an interval of 3 seconds followed by a further coupled beat.

The *electro-encephalogram*, which was recorded simultaneously, was entirely normal except that after a period of asystole there were minimal change in rhythm due to cerebral anoxæmia. This investigation was carried out by Dr. J. D. N. Hill, for whose help I am grateful.

The following observations were made.

Effect of exercise. This was always followed by an increase of pulse rate for some seconds, but this was usually succeeded by periods of asystole. Very slight exertion caused extrasystoles or coupling and the pulse was always markedly irregular on these occasions. Rising from a lying to a sitting position ten times caused a very transient rise to 60 beats a minute. If the patient held her breath for 15 to 30 seconds similar irregular pulsation with gaps would occur.

Compression of carotid sinus. This had absolutely no effect on the pulse rate or blood pressure on a number of separate occasions when it was tried.

Effect of atropine. 1/50 of a grain of atropine was injected intravenously on 8/2/44. The pulse rate before the injection was regular at 20 a minute. After ten minutes the pulse rate had risen to 27, after fifteen to 31, after thirty to 31, after forty-five to 33. The mouth was then dry and the pupils widely dilated. The pulse rate remained at 33 to 34 until three hours after the injection and then gradually fell.

On 19/5/44, 1/25 of a grain of atropine was given intravenously. The pulse rate was regular at 20 before the injection. After five minutes it had risen to 34 beats at the apex. These were coupled and only 17 were counted at the wrist. This coupling continued for fifteen minutes. After twenty minutes the rate was regular at 32 at the wrist and apex. The vision was blurred and the mouth dry: after an hour the rate had risen to 34 and was regular. It continued at this height for several hours, but six hours after the injection had fallen to 25.

It was noticed that the blood pressure, which was 168/90 before the injection, rose to 212/90 after half an hour, to 208/90 after forty minutes, and had fallen to 190/90 after two and a half hours. As a result of this injection the patient suffered from transient mild symptoms of atropine poisoning and was hallucinated and disorientated.

Atropine in full doses, therefore, caused a slight increase in rate with a regular pulse. Medicinal doses (1/100 of a grain and regular heavy doses of belladonna) given when the patient was having frequent attacks of faintness had no obvious beneficial effect. The patient thought that periods of asystole were rather more frequent during this treatment.

Effect of injection of adrenalin. 5 minims of adrenalin was injected subcutaneously on

4/2/44. The pulse rate before the injection was 20. It rose to 27 after twenty minutes and was somewhat irregular at this time due to extrasystoles. On 29/10/44 the pulse was regular at 19 at the wrist, but with coupled beats audible at the apex for fifteen minutes before 5 minims of adrenalin were given. After five minutes the patient was trembling slightly but the pulse rate was unaltered and the beats were still coupled; after seven minutes 22 coupled beats were counted, after nine minutes 28; at eleven minutes the pulse became irregular with asystole of seven seconds followed by six or seven rapid beats. No further rise in rate occurred but the pulse became more irregular and periods of asystole of 5–7 seconds occurred once or twice each minute until half-an-hour after the injection, when the pauses ceased, coupled beats diminished, and a regular rhythm of 24 beats to the minute was observed twenty-seven minutes after the injection. Occasional coupled beats were felt after this but after 42 minutes the rate was regular at 28, and after 45 at 24 a minute.

Adrenalin, therefore, appeared to produce an effect resembling that of exercise, leading to a slight increase of rate, with periods of asystole.

Effect of ephredrine. Ephedrine, 1/2 grain given by mouth on 10/2/44, was apparently followed by some increase in the number of extrasystoles, although the pulse rate, which was 19 before administration, never rose to more than 22 during the next hour.

Effect of thyroxin. Thyroxin, 2 mg., was given intravenously on 7/5/44. The pulse rate beforehand was 18 and regular; blood pressure 152/80. After ten minutes the pulse rate was 16 and regular; after twenty minutes, 16 regular; after thirty minutes, 19 with three extrasystoles, systolic blood pressure 156; after forty minutes the pulse rate was 17 with 4 coupled beats. After an hour the pulse rate was 19 with 3 coupled beats; after 2 hours, 20 with 3 coupled beats; after 3 hours, 22 and regular. The rate continued between 23 and 24 for a number of hours. This dose of thyroxin had no obvious effect on the pulse rate.

The administration of acetylcholine or its derivatives was considered too dangerous owing to the possibility of increasing the periods of asystole. Their effect was not, therefore, observed.

The following drugs were given therapeutically. *Tinct. Belladonna*, up to 20 minims, four-hourly, had no obvious effect on the pulse rate but made the patient dry and uncomfortable; during the time she was on this preparation she had many faint turns. Injection of *atropine*, 1/100 of a grain, was likewise ineffective in preventing attacks of asystole. *Thyroid sicca*, 1/4 of a grain t.i.d., had no effect. *Barium chloride*, 1/2 a grain t.i.d., *Luminal*, 1/2 a grain t.i.d. by mouth, *Nicotinic acid*, 100 mg. daily, and *Benerva*, 50 mg. daily, given intravenously, had no obvious effect on the pulse rate. It was thought that the atropine preparations and the thyroid possibly led to an increase in the irregularity of the pulse and in the number of faint turns.

Discussion

Loss of consciousness with disappearance of the pulse at the wrist and absence of heart sounds is commonly due to one of three clinical conditions—simple fainting resulting from vaso-vagal disturbances, heart block (Stokes-Adams disease), or stimulation of the vagus nerve as the result of a sensitive carotid sinus reflex or more rarely by pressure from a tumour or aneurysm. The patient whose history has been recounted did not suffer from any of these conditions. Simple fainting is unlikely to occur at rest in bed, particularly during sleep, nor were the usual prodromal symptoms of salivation and perspiration ever recorded; there was no cardiographic evidence of heart block; the symptoms could not be reproduced by pressure over the carotid sinuses, nor were they prevented by atropine. Moreover, none of these conditions offers any explanation of the persistent bradycardia (varying between 15 and 30 beats a minute) known to have been present for seven months while the patient was in hospital and probably for at least two years.

Other rare causes of cardiac syncope have been described. In sino-auricular block, Type A (Cowan), the sinus stimulus may default so that auricles and ventricles miss one or more beats, and fainting may occur. The interval between successive beats is in this case always a multiple of the normal beat, i.e. it may be two, three, or four times the normal interval between auricular contractions. The pulse rate in S-A block is usually within normal limits,

but Cowan records the history of a man, aged 63, who suffered from syncopal attacks and had a basic heart rate of 30 due to a sinus bradycardia. This was thought to be the result of impaired blood supply of the S-A node following coronary infarction. Although this case is in many ways similar to ours, the absence of any regular mathematical relationship between the periods of asystole and the preceding pulse rate excludes sino-auricular block in the latter.

Laslett (1908–09) described the case of a woman, aged 40, suffering from fainting attacks due to arrest of the whole heart, as demonstrated by sphygmographic tracings of the jugular pulse. In this patient the basic rate was 60–70 beats a minute. Unconsciousness occurred if asystole lasted for more than 7 seconds. The irregularity of the intermissions in this case excludes S-A block. After atropine, 1/50 of a grain subcutaneously, the pulse rate rose to 100 and remained regular for a number of hours: exertion or excitement also temporarily prevented periods of asystole. Laslett concluded that increased vagus influence was responsible for the failure of the S-A node in this case.

Wedd also records the history of a boy, aged 16 years, complaining of fainting, in whom the heart rate varied between 32 and 86 with periods of standstill of from 3–7 seconds. The electrocardiogram showed, however, that the heart beat originated from the A-V node. This nodal rhythm persisted after atropine (1/33 of a grain), but periods of asystole were abolished and the pulse rate rose from 40 to 86. The periods of cardiac standstill appear to have been due to excessive vagal stimulation.

Trocmé (1922) describes two cases of sinus bradycardia with no increase of rate following atropine, and attributes the condition to hypo-excitability of the S-A node. Periods of asystole occurred, which he attributed to increased vagal tone.

This patient differs from most others with cardiac standstill due to rare disturbances of rhythm in the failure of atropine to abolish the periods of standstill or to raise the basic pulse rate to a normal level. This striking ineffectiveness of stimulation or paralysis of the vagus nerve to modify the heart's action suggests that the S-A node is less excitable than normal. The slight effect of exercise and other drugs, such as adrenalin, thyroid, or barium chloride is further confirmation of this view. Trocmé's cases alone may have had a mechanism similar to ours.

The reason for the development of a condition of such reduced excitability remains obscure. There was some evidence that psychological factors might influence her condition, but it is unlikely that the condition could be explained on this basis. In view of the patient's age, diminution of the blood supply to the region of the pacemaker as a result of atheroma seems to be the most probable cause. On the other hand the failure of the A-V node or of the ventricle to initiate their own rhythm during periods of prolonged asystole may indicate a general condition of hypo-excitability.

Summary

A case of persistent sinus bradycardia with syncopal attacks due to cardiac standstill is described.

Evidence is given for believing that this is not vagal in origin but due to hypo-excitability of the pacemaker.

I should like to thank Dr. Terence East and Dr. Parkinson for their helpful advice.

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LIGATURE OF PATENT DUCTUS ARTERIOSUS

BY

GEOFFREY BOURNE

Received February 6, 1945

The effect of ligation on infection of the patent ductus has been admirably summarized from the surgical point of view by my colleague, Mr. O. S. Tubbs (1944). His paper, which gives a valuable account of the anatomy, physiology, and pathology of the ductus arteriosus, is based upon nine infected cases, eight of which were treated by us in collaboration. The purpose of the present paper is to discuss certain medical aspects of these cases and of two additional non-infected cases, also submitted to operation. Details of the individual infected cases are already published in Mr. Tubb's paper, and are referred to here by the same numbers as those used in that paper and in that of Bourne, Keele, and Tubbs (1941).

Infected Cases

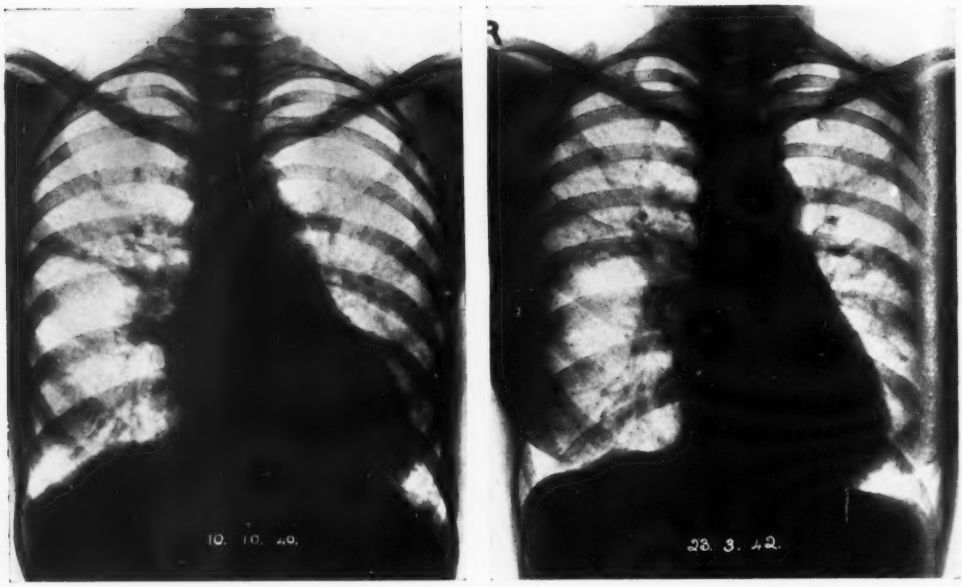
Dr. Keele's case, Case 1 of our series (Bourne, Keele, and Tubbs, 1941) was the first infected case recorded that was cured by ligature of the ductus arteriosus. The date of the operation was December 5, 1939. Of the first five patients of our series, four are alive and well, from five to three years after the operation, with no recurrence of symptoms, of infection, or of cardiac disability. The permanent value of the operation is thus proved.

The infecting organism in Case 1 was *H. para-influenzæ*, and in seven other cases it was *Streptococcus viridans*. In one case (Case 8) the infection was apparently mixed, *Staphylococcus aureus* and *Streptococcus viridans*.

Although the number of cases is not large, certain observations, even if made in a single case, are so significant as to be worth recording, and may even form the basis of legitimate deductions. The extent to which these deductions are true, and the proportion of cases in which the observed phenomenon occurs must, of course, be determined by the study of a much larger number of cases.

Heart Size. The late result of ligature on the heart size is well shown in the X-ray photographs taken in Case 2 (Fig. 1). The first picture, dated October 10, 1940, shows an enlarged heart, the transverse diameter of the heart measuring 14·25 cm. and that of the thorax 24·75 cm.; it also shows typical enlargement of the pulmonary conus. The second picture, dated March 23, 1942, shows the transverse diameter of the heart to be 12·25 cm. and that of the thorax 24·75 cm.; the heart contour has become normal and the conus is no longer enlarged. This shows that ligature of the patent ductus can cause a reduction in heart size similar to that observed by Drury (personal communication) in animals in which an experimental arterio-venous aneurysm had been produced, and by Hitzig (1935) after ligature of arterio-venous aneurysm in man.

Thrill and Murmur. The classical thrill and murmur are generally ascribed to the rapid flow of blood from the aorta to the pulmonary artery. This presumably occurs when the aortic pressure is higher, i.e. during systole and early diastole. Compression of the patent ductus during operation obliterates the thrill in nearly every case, and this largely confirms the above theory of its causation. The following observations suggest that this explanation is not complete. Firstly, in Case 2, application of one ligature only reduced, but did not abolish, the thrill; this disappeared only after a second ligature had obliterated more of the lumen of the ductus. Secondly, in the same case, the diastolic murmur at first disappeared,



A B

FIG. 1.—Reduction in size of the heart after ligature of the patent ductus arteriosus (m.t.d. reduced from 14·25 to 12·25 cm.). (A) 10/10/40. (B) 23/3/42.

but returned, much less in volume, seventeen months after ligature, although the transverse diameter of the heart had diminished by 2 cm., and although the blood pressure remained perfectly normal (Fig. 1). Thirdly, in Case 4, the diastolic murmur disappeared for two weeks and then fully returned; yet, at the post-mortem examination seven weeks after operation, the pulmonary end of the ductus was found to be so blocked by a massive clot that water injected into the aorta failed to pass. There was, however, an aneurysm of the ductus, patent to the aorta and 3 cm. in diameter. Finally, Shirley Smith's observations (1929) on cases of patent ductus in infants, in which the typical thrill and murmur were absent during life, may be relevant to this problem.

The general deduction would appear to be that, although the thrill and murmur are largely caused in the usually accepted fashion, this is not the whole explanation. Patency of the ductus may occur without these signs, and these signs may be present without patency, although such conditions are exceptional.

The Blood Pressure. Immediately after ligature, a great rise in the diastolic and a lesser rise in the systolic blood pressure was observed. The figures for the changes in diastolic pressure (in mm. of mercury) in the first six cases were as follows: Case 1, from 60 to 120; Case 2, from 40 to 122; Case 3, from 58 to 108; Case 4, from 56 to 90; Case 5, from 64 to 98; Case 6, from 52 to 102; the average rise being from 55 to 107. This diastolic increase above normal may last for some weeks (Bourne, 1941), and therefore it is probably due to factors other than the increased blood volume. The cardiac hypertrophy, or an increased peripheral vascular tone, or both, may be causative factors. An associated state of temporary renal failure has been noted (Bourne, 1941). The sudden blood pressure change did not cause symptoms in any of the patients.

The Effect of Ligature upon Infection of the Ductus. Ligature is the only proved curative measure available. Without it the condition is usually fatal. Only two cases of recovery without treatment by ligature are on record (Chester, 1937; and Touroff and Tuckman, 1942). Of the present series of nine infected cases treated by ligature six are alive and well, from five to nearly two years after the operation. The results obtained in Case 5 demonstrate that ligature of the ductus can, of itself, bring about the disappearance of the infection,

for in this case all other forms of treatment were withheld. Seven days after ligature, the patient became completely afebrile, and the blood culture, which had previously been positive, showing the presence of *Streptococcus viridans*, became negative and remained so.

The Effect of Chemotherapy. The results obtained by the use of drugs were disappointing. In one case only (Case 2), sulphapyridine sterilized the blood and removed the fever for the twelve day period preceding operation. In Case 1, where infection was due to *H. parainfluenzæ*, sulphapyridine was ineffective. In six cases of infection by *Streptococcus viridans*, sulphanilamide, sulphapyridine, sulphathiazole, sulphadiazine, and sulphamezathine given in full doses produced no effect. One or more of these drugs was tried in each case. In one case (Case 8) infected by *Staphylococcus aureus* sulphathiazole failed.

This suggests that no advantage is obtained by instituting chemotherapy before operation if the condition of the patient is reasonably good. Chemotherapy, however, should be used to modify the severity of the toxæmia, before operation, in patients who are critically ill. It is also of value after operation, when infection persists. Infection may persist at the pulmonary end of the ductus, or in metastic and embolic infection in the lung. Chemotherapy, clearly, should be tried also if the post-operative fever is due to infection of the mitral or aortic cusps, although here the effect is problematical.

Prognosis in Cases Treated by Ligature. The ultimate prognosis is good, considering the seriousness of the condition. Experience in the surgeon and skill in the anæsthetist are, of course, vitally important. From the small series of cases here recorded certain ideas concerning prognosis suggest themselves.

The degree of illness is a clinical matter, and is hard to evaluate scientifically. But in Case 3 the patient was desperately ill, and by ordinary criteria was an unsuitable subject for a surgical operation. None the less this was decided upon, and the patient made a good recovery. The comparatively small risk of operation in these ill and toxic patients is also stressed by the fact that no death occurred on the table. One patient died 45 minutes after the operation. The other two fatal cases, both of whom had severe secondary pulmonary sepsis from infected pulmonary emboli, survived the operation by seven weeks and by four months respectively.

It may be significant that Cases 4 and 7 had marked cardiac enlargement ; both died. In Case 9, the other fatal case, the heart was only slightly enlarged, and infection of the aortic valve was present.

Pulmonary embolism and infarction in this condition is of two varieties, that occurring from the growing vegetations, and that resulting from the fragmentation of clots or vegetations during the healing process. The former occurs before, and the latter after operation. Pre-operative embolism, with pleurisy, either with radiological change or visible or palpable at operation, was present in seven of the nine infected cases. Its presence, therefore, does not seem to influence the prognosis. Post-operative embolism in convalescence is common and is equally free from serious danger.

In two of the three fatal cases, an aneurysm of the pulmonary artery (3 cm. in diameter in Case 4, and 1·5 cm. in diameter in Case 9) together with multiple pulmonary infarcts was present. In two fatal cases, left-sided endocarditis was found at autopsy, aortic endocarditis in Case 7, and mitral and aortic endocarditis in Case 9.

The increased virulence of infective endocarditis in children also seems to influence the outlook in the case of this lesion. The two youngest patients, aged 10 and 15 years, died.

These factors must all be remembered in estimating the possible result of operative treatment.

Ligature of Non-infected Cases

A large number of uninfected cases have been treated by ligature and have been reported by several authors. Indications for this operation would seem to be mainly:

(1) the anticipation of subsequent infection,
(2) the threat of heart failure, or
(3) in children, the failure to grow normally.

It is highly probable that the risk of subsequent infection can be prevented by this operation.

The figures given by Maud Abbott (1936), showing that infection developed in 29 per cent of 73 cases over the age of two years, suggest that the chance of subsequent infection is great. It is also true that the operative risk is less in the uninfected cases, the uninfected ductus being less fragile. On the other hand, the procedure is not without danger. Future developments in chemotherapy, or treatment by penicillin, may strengthen the conservative attitude of watching such cases and reserving surgical treatment until the actual onset of infection. This is the writer's policy in this matter at present. [Since the date of writing one case treated with penicillin, before operation, became afebrile in 36 hours.]

The two following cases have not been described previously. In one, a woman of 2 years of age, heart failure was present. The history was that she had always been short of breath on exertion, and that this had been increasing slowly up to the point when she would have to stop after climbing about five steps. Orthopnœa had also been present. Three months previous to operation, œdema of the feet and legs had appeared and had been increasing. The lesion was considerable, for the heart was large. The heart diameter was 15 cm. and that of the chest 30·5 cm.; the blood pressure was 140/54. Since operation she has been better than ever before in her life. During this period of one year and seven months she has done war work for nine hours daily in a factory, often including Sundays. She was able to remain at work for six months of pregnancy without symptoms. She had previously had two children, but her life had been that of a partial invalid. Thus, ligature of the ductus would seem to be indicated for the relief of early congestive failure.

The other case was that of a child of nine years. She was symptomless, but was undeveloped for her age compared with two older brothers, and the heart was a little enlarged. Her father, a doctor, had a lively realization of the risk of infection. In this combination of circumstances operation was decided upon. Unfortunately, the ductus was of the stoma or " window " type, having no length at all. This rendered ligature impossible. The danger of the ductus being of the stoma or " window " type must be taken into account in assessing the operative outlook, either clinically or in discussion with patients or relatives both in infected and in non-infected cases.

Conclusions

In infected cases of patent ductus arteriosus, successful ligature of the ductus brings about a lasting cure.

In non-infected cases (of which I have less experience) it may be most successful even at the stage when heart failure is developing.

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LIGATION OF THE PATENT DUCTUS ARTERIOSUS

BY

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This operation is now being performed to cure patients who have become infected, but also it may be done to remedy a congenital defect, which very considerably reduces the prospects of longevity, and is as well the source of several serious disadvantages.

This is an account of the experience provided by thirteen cases, considered from the medical point of view. All the operations were done by Mr. John B. Hunter, F.R.C.S., and Dr. Nosworthy gave the anæsthetic.

Diagnosis and Prognosis

Diagnosis presented no difficulty: the typical murmur, best heard in the second left intercostal space, starting just after the first sound and persisting into diastole (with the exception of one case where it is doubtful whether it would be heard beyond the second sound), was present in all. This applies to two other cases seen during the same period, who declined operation. Its hollow whizzing character resembles nothing else to my ear. Is not " machinery murmur " a bad expression? I cannot think of any machine causing such a sound. In most a thrill was palpable as well. Sometimes there was a systolic pulsation, and as a rule the pulmonary second sound was loud and the closure palpable. The pulmonary artery was never large enough to cause dullness. The possible presence of another congenital defect, in particular pulmonary stenosis, was always considered but was never suspected. A normal cardiogram, and the absence of its peculiar murmur lower down should exclude pulmonary stenosis. Obviously, if this were present, ligation of the ductus would be undesirable.

All the cardiograms were within normal limits.

Enlargement of the pulmonary artery in the skiagram may be quite conspicuous, but in this series of thirteen cases it is clear from the outlines shown in the figure that nothing very striking may be noted. In Case 4 the pulmonary artery was largest, and that has a flat curve.

Enlargement of the heart was present only in Case 3 and perhaps in Case 2. But in this series the disease was in its early stage, and failure had in no case come on. The blood pressure readings showed no constant abnormality, but an average figure of 120/70 indicated a slightly increased pulse pressure. In some the diastolic pressure tended to be low.

Physical examination before operation gave no reliable information as to the size and shape of the ductus.

Probably in most cases, until well into adult life, a patent ductus arteriosus may interfere but little with activities. But such a lesion as this is almost certain to be recognized early in life, and in many instances restrictions that are probably unnecessary are imposed. The result is that the patient is well aware that there is something wrong with him, and may become unduly heart-conscious and even neurotic. He will certainly miss a great deal of the best that youth can give.

Later on more serious considerations arise. Employment in many walks of life will be hard to obtain. The Services, civil and military, will be closed to him; banks and many firms will not employ him because he is ineligible for staff schemes and pension funds. Life assurance will be denied him. Strenuous occupations will be unwise; a woman may be

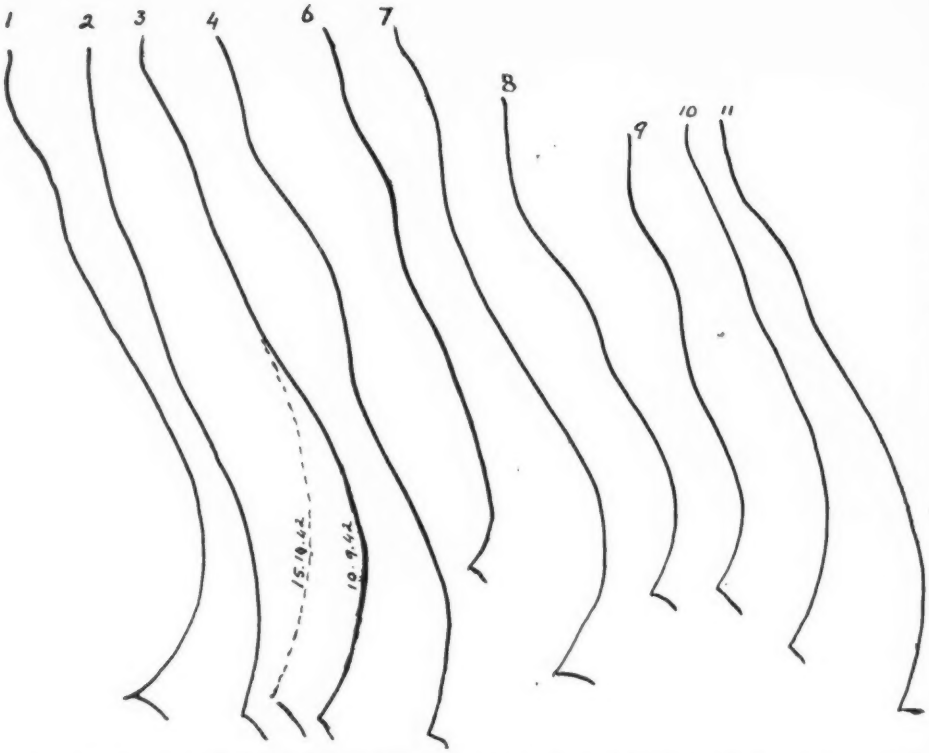

FIG. 1.—Outlines of the left border of the hearts, before and after operation, in patent ductus arteriosus. The numbers correspond with those of the cases.

advised against marriage and certainly against pregnancy, although she would probably accomplish this well enough.

Ultimate Prognosis. The danger of infection in these patients is considerable. Although for the most part they seem to reach the twenties without disability, they are rarely seen in middle age. I cannot recollect having seen one over the age of forty. Heart failure no doubt accounts for the early death of many.

CHOICE OF OPERATION AND RESULTS

The experience of this small series makes one conclude that ligation of the patent ductus arteriosus by a surgeon skilled in thoracic surgery, aided by an anæsthetist who has practised the technique that this work requires, is not a dangerous procedure. The small pneumothorax or hydrothorax, which sometimes appeared, very soon cleared up with the help of breathing exercises. In no case was there any anxiety about the patient after the operation. Breathing exercises were always given on or soon after the third day. Unquestionably the children were least affected, and tolerated the operation very well.

Age for Operation. Any time in childhood, as soon after the sixth year as possible for preference, seems to be the best. I believe that my colleague, Mr. Hunter, who is describing these cases elsewhere from the surgical point of view, is of opinion that for technical reasons the operation is easier in children. Certainly it would be an advantage to cure this defect as soon as possible in order that its undesirable effects on mental and physical development may be eliminated while the child is growing. It is obviously a good thing to have as normal a childhood as possible.

In all these patients the signs of the patent ductus disappeared (with one exception, for reasons given). It was the practice of Mr. Hunter, before ligation, to press on the ductus with his finger and note the disappearance of the thrill. This was always there, even if it could not be felt on the chest wall.

The contour of the heart showed very little change in subsequent skiagrams, except in Cases 2 and 3 where the ventricles decreased a little in size, and in Case 9 where the curve of the pulmonary artery became a little flatter. In these cases, where before ligation no gross degree of abnormality was apparent, little change is to be expected.

Effects of Operation. The young adult is certainly relieved to feel that his disability is cured, and that his heart is normal, although, of course, he does not know his medical prognosis. To be free from the various disadvantages detailed above is obviously a benefit.

Whether there remains any risk of infection on the dimple that I suppose persists at either end of the ligated ductus, one cannot yet say. One must not press the analogy too far, but infection on the pits and excrescences of an atheromatous aorta is very uncommon, and primary infection on the right side of the heart is very rare. The favourite site for infection is where blood passes through a small hole. For instance, organisms attack the patent septum of Maladie de Roger often enough, but not that found in Fallot's tetralogy.

One may hope that the risk of infection after ligation is negligible.

In some children a patent ductus arteriosus seems to retard mental and physical development, and it must be desirable to obviate this.

To leave operation until heart failure has set in, when the patient is probably well into adult life and the procedure less easy and more risky, is surely a mistake. To wait until infection has occurred is dangerous, for although brilliant cures have been effected, they cannot be relied on.

Summary

Ligation of the patent ductus arteriosus has been performed in thirteen cases. No anxiety arose in any case following operation. One patient, infected before operation, died later. One other patient died of septicæmia which started after nine days normal convalescence. It may possibly have arisen as a result of the operation, but there were no direct evidence of this.

The conclusion is that ligation is a good method of treatment in any patient with patent ductus arteriosus; the sooner after the sixth year, the better.

Appendix of Case Notes

Case 1. Male, aged 16. Drayman's apprentice. He was of rather poor physique and somewhat slow mentality. He had lived an ordinary life without symptoms, but had been rejected by the Air Training Corps Board.

A typical murmur was heard above the pulmonary area just after the first sound, extending faintly into diastole. There was no thrill. The pulmonary second sound was loud. The pulmonary artery was enlarged and there was a slight pulsation in the hilar vessels. The heart was not enlarged. B.P. 144/40–135/80. Electrocardiogram (EC.) normal. There was functional albuminuria. Blood urea, 24 mg. per 100 c.c. Specific gravity test and urea clearance were normal.

At operation the ductus was estimated as being about 10 mm. × 6 mm. The thrill over it disappeared at once on pressure, and permanently on ligation.

After operation the pulse rose to 140, but was down to 80 on the fourth day. The blood urea rose to 41 mg. per 100 c.c. on the fourth day, but fell to 22 mg. per 100 c.c. on the seventh day. A small local pneumothorax appeared at the left apex and a small hydrothorax at the left base. These cleared up in the following three weeks, breathing exercises being given as soon as possible.

He left hospital eight weeks after operation, having gained 4 lb. The ductus murmur had disappeared, though a faint systolic was heard for a time. He seemed to be much more lively towards the end of his stay. At no time was there any anxiety about him and he tolerated the operation well. When seen again three years and nine months later, he was a flight-sergeant in the R.A.F., shortly to undertake operational duties. The skiagram showed no change in the cardiac outline. B.P.120/80.

Case 2. Female, aged 18. Clerk. She had never had any symptoms, but since the discovery of the lesion at the age of five, had been kept from strenuous activities She was well-built and of normal mentality. She had been referred by a medical board under the Military Training Act.

A typical murmur, occurring late in systole and persisting through diastole, was audible in the second and third left spaces. A thrill was felt. The pulmonary second sound was loud. The heart was not enlarged (12·25 cm. in diameter) but the pulmonary artery was a little full. B.P. 120/70.

At operation the ductus seemed to be about 10 mm. × 6 mm. The thrill disappeared at once on pressure and ligation. Afterwards the pulse did not rise above 110. A small hydrothorax appeared at the left base. Blood urea on third day, 26 mg. per 100 c.c. She was up on the twelfth day and left after five weeks, the fluid having quickly disappeared. Only a faint systolic murmur could be heard in the pulmonary area. The case gave no anxiety at all.

When seen two and a half years later she was very well, and particularly pleased to feel she was normal. The contour of the pulmonary artery was unchanged; the transverse diameter was 11·75 cm. B.P. 110/80.

Case 3. Female, aged 25. Lift attendant. The lesion had been found in childhood and she had lived a somewhat restricted life, with liability to undue dyspnœa. She had been referred under the Military Training Act. She was of normal build and mentality.

The usual typical thrill and murmur were present, with a loud and palpable pulmonary closure. The heart was somewhat enlarged, transverse diameter 13·5 cm., and the shadow of the pulmonary artery was slightly increased. B.P. 120/50, 120/80. EC. normal. Kidney function normal.

The operation (24/9/42) was followed by no complications, and there was but little discomfort. The pulse did not exceed 110, and she left in a month. The murmur had completely disappeared.

Two months later she felt very well, and was pleased to be normal. The transverse diameter of the heart was 12·5 cm. and the shadow of the pulmonary artery was a little smaller. Probably as a result of enemy action, it has been impossible to trace her, for her home has been destroyed.

Case 4. Female, aged 31. Lorry driver. She had always been breathless on anything more than slight exertion, and had never played any games. Lately the dyspnœa and palpitation had been worse, but this was probably mainly due to hypochromic anæmia (66 per cent Hb.).

There was a characteristic low-pitched persistent murmur, with thrill, and some systolic pulsation above the pulmonary area, with a very loud second sound. The pulmonary artery was rather large. The transverse diameter was 12·25 cm. B.P. 120/85. Kidney function normal. EC. normal.

The thrill ceased when the ductus was tied. After operation the pulse rose to 120 on one occasion. A small effusion formed in the mid-zone but soon cleared, and she left after a month. A slight systolic murmur persisted.

When seen twenty-six months later she was very well, and free from dyspnœa. The transverse diameter and the curve of the pulmonary artery were unchanged. B.P.120/90. No murmur was heard.

Case 5. Female, aged 10. (*Dr. C. Shaw.*) A thin, puny child, not robust, weighing 45 lb. Mentally very alert and intelligent. She had had no symptoms, except liability to asthma.

There were the typical murmur and thrill of a patent ductus arteriosus, with loud palpable pulmonary closure. The heart appeared to be slightly enlarged. B.P. 110/56–120/70. EC. normal.

Before operation the heart rate was very unstable, varying between 130 and 80. After operation there was an increase to 160 for a short time; but the rate soon settled and was much steadier than before. The ductus was funnel-shaped, base towards pulmonary artery, and about 7–9 mm. wide and 11 mm. long.

The signs of patent ductus disappeared after ligation, only a faint systolic whiff being audible. A small pneumothorax at the left apex and small effusion at the left base cleared up in a fortnight with the help of breathing exercises, and she left hospital three weeks after operation, having gained nine pounds in weight. The case caused no anxiety for the operation was well tolerated.

Two and a half years later her mother reports that she is very well, growing fast and learning tap dancing. She now weighs 82 lb.

Case 6. Female, aged 9. (*Dr. W. Sheldon.*) Thin asthenic child, weighing 54 lb., of normal mentality, eighth in family. There had been no symptoms, and she had played the usual games.

There were the typical murmur and thrill of patent ductus, with very loud and palpable pulmonary closure. The pulmonary artery was enlarged but not the ventricles. EC. normal. B.P. 120/60.

For a few hours after operation the heart rate was 140, but it soon settled. There were no complications and she left hospital on the fifteenth day. The murmur had completely disappeared.

When seen two years later she was well. The parents were particularly pleased with her progress at school, where she had recently won a scholarship. Her intelligence quotient rose 21 points five

months after operation. She had become more lively and active. She now weighed 69 lb. B.P. 140/60. Radioscopy showed that the pulmonary artery now had a normal contour.

Case 7. Female, aged 21. (*Dr. J. Maxwell.*) Well-developed young woman of rather neurotic mentality. Her activities had always been restricted, and latterly she had been too breathless to do much.

There were the harsh continuous murmur and thrill of patent ductus above pulmonary valves; there was no cardiac enlargement, and the contour of the pulmonary artery was normal. B.P. 110/85. EC. normal.

At operation the ductus was found to be short and wide. The next day the murmur had gone. Breathing was easy, the pulse did not exceed 100. She left hospital twenty-four days after operation; there were no pulmonary complications.

Six months later she could do more; skiagram of heart unchanged in outline. Nineteen months after operation she had not started work, but that seemed to be due to her cardiac neurosis.

Case 8. Male, aged 6. (*Dr. W. Sheldon.*) An active child in good condition, weighing 55 lb.

Above the pulmonary area there was a characteristic continuous murmur of a patent ductus, with slight systolic pulsation and a loud second sound. There was a slight suggestion of a pulmonary reflux. No thrill was palpable. The heart was not enlarged, but the pulmonary artery showed some enlargement. EC. normal. B.P. 110/65.

After operation the heart rate rose to 130 for a day or so. He was very little affected. Breathing exercises were given and he was up on the seventh day. There were no pulmonary complications. He left after eight weeks in hospital, having gained 4 lb. The murmur disappeared at once, but an endocardial click persisted.

When seen eighteen months later the shadow of the pulmonary artery was unchanged, but the closure was no longer palpable. He was very well and had grown a good deal.

Case 9. Male, aged 6. (*Dr. W. Sheldon.*) A small, dull child, weighing 35 lb. There had been dyspnœa on exertion.

Above the pulmonary area there was a continuous murmur of patent ductus. The heart was not enlarged; the curve of the pulmonary artery was slightly increased.

The operation was done under avertin. Afterwards the pulse rose to 130 for two days. There was slight surgical emphysema and some transient collapse at the left base. This soon cleared up with breathing exercises, and he left hospital on the tenth day.

Nine months later his parents wrote saying that he weighed 40 lb., and that his breathlessness had gone; and that he seemed much more grown up since the operation and was very quick at school.

Case 10. Male, aged 7. (*Mr. J. Hunter.*) A small boy, dull and slow and backward mentally, weighing 60 lb. A typical murmur was heard, but no thrill was felt; the pulmonary second sound was not particularly loud: there was no pulsation. Heart was not enlarged. B.P. 115/85. EC. normal.

The operation was followed by no complications and he left hospital on the seventeenth day. The murmur had entirely disappeared.

This case is too recent for any subsequent progress to be of interest yet.

Case 11. Female, aged 12. (*Dr. W. Sheldon.*) Some complaint of breathlessness and palpitation: found she had to stop doing things before the others in the physical training class. A well-built girl, weighing 7st. 4 lb.

The murmur was hardly audible in diastole. There was no thrill. The heart was not enlarged (transverse diameter 11 cm.). B.P. 135/70. EC. normal. Pulmonary artery rather large in skiagram.

At operation the ductus was found to be large. The pulse reached 120 for one day, but soon subsided. A small hydropneumothorax followed, with some infection needing sulphapyridine, but it was quickly controlled. She left hospital on the twenty-fifth day. A year later she was reported to be very well, and had gained 10 lb.

Case 12. Female, aged 5. (*Dr. W. Sheldon.*) A small, thin child, weighing 30 lb. Her mentality was normal for the age.

The characteristic thrill and murmur were present, just above the pulmonary area. B.P. 100/55, 100/70. The heart was not enlarged, and the pulmonary contour normal. EC. normal.

After ligation the thrill at once disappeared, and later the murmur was found to have gone. Breathing was easy though the pulse reached 120. No complications occurred; but on the tenth day a high fever started, which was found to be due to staphylococcal septicæmia. Of this she subsequently died, in spite of sulphonamides and penicillin. No post-mortem examination was allowed; the

source of the infection remained obscure: whether as regards the operation it was "post" or "propter" cannot be said, but such infections not uncommonly arise without apparent cause, and for ten days nothing went amiss.

Case 13. Female, aged 26. This patient came in with infection of a patent ductus arteriosus. This had started about the time of a tooth-extraction two months before. The infection was due to *Streptococcus viridans*. The usual murmur and thrill were present. B.P. 155/65. The heart was not enlarged.

The ductus was ligated without complications. For a few days the murmur disappeared but later it returned. Infarcts appeared in the lungs, and the signs of an infection of the aortic valves were detected. In spite of courses of sulphonamides she ultimately died. At autopsy it became clear what had happened. The ductus was not effectively closed because it was too full of vegetations. The pulmonary artery and valves were extensively affected, and there were vegetations on the aortic valves. The murmurs that again became audible arose from the imperfectly occluded ductus and later from the diseased pulmonary artery and valves and from the aortic valves.

The fatal ending in this case is an argument in favour of prophylactic ligation.

MORPHINE HYPERSENSITIVITY IN KYPHOSCOLIOSIS

BY

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From St. Thomas's Hospital

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It has been recognized since the time of Hippocrates that patients suffering from " hump back " die young. The first descriptions of early death in persons suffering from severe kyphoscoliosis did not incriminate the cardiovascular system, and it was not until the end of the last century that continental observers described heart failure as being the most frequent cause. In 1930, Coombs made one of the first contributions to the English literature in a paper entitled, " *Fatal cardiac failure in persons with angular deformity of the chest.*" More recently, in America, Chapman, Dill, and Graybiel (1939) have investigated twelve such cases, and in a review of others reported, showed that the average age at death was only thirty years. The purpose of this communication is to describe three patients whose deaths while in cardiac failure are believed to have been precipitated by the administration of morphia.

Case Notes

Case 1. Male, aged 36; a hunchback as long as he could remember. He attended a school for physical defectives, but nevertheless played cricket and football. After leaving school, he led a comparatively normal life as a costermonger until the age of 30, when he was admitted to hospital complaining of increasing dyspnœa on exertion, and of hæmoptysis.

On examination, a gross mid-dorsal kyphoscoliosis to the right. Pulse 86, regular. Slightly cyanosed. Neck veins engorged to within one inch of the angle of the jaw. Fine crepitations at both bases. Moderate œdema of both ankles. Liver palpable, but not tender. Heart enlarged to the right and left. Heart sounds normal. No murmurs. Blood pressure, 180/130. Retinæ normal.

He was treated with Guy's pill and mercurial diuretics, and discharged three weeks later, having recovered from his failure. He felt well, and was working for two-and-a-half years before he was again admitted in failure. He was then orthopnœic, with a regular pulse rate of 90, and a blood pressure of 170/140. An X-ray photograph of his chest showed marked enlargement of both ventricles, and pulmonary congestion. An electrocardiogram was within normal limits. On the evening of his admission, he was given oxygen by B.L.B. mask, and morphia, 1/4 of a grain, for the first time, The respirations became increasingly shallow, and death occurred in one hour.

Post-mortem examination. Heart weight, 606 g. Both ventricular walls markedly thickened. Moderate atheroma of the pulmonary arteries. Coronary arteries and aorta normal. Lungs: left more emphysematous than right; both congested.

Case 2. Male, aged 36. He complained of increasing dyspnœa for two months. His back had begun to be " humped " at 24 years of age. This had gradually increased to reach its present severity six years ago.

On examination, orthopnœic, with cyanosis. Ventricular rate 88, auricular fibrillation. Neck veins engorged; marked œdema of legs and sacrum; crepitations at both bases. Heart enlarged one inch to right of sternum. Pulmonary second abnormally loud. No murmurs. Blood pressure 110/70. Retinæ normal. A very marked mid-dorsal kyphoscoliosis to the

right. A cardiogram confirmed auricular fibrillation, and showed right ventricular preponderence.

He was given 2 c.c. of mersalyl intravenously, and oxygen by B.L.B. mask. On the night of admission, morphia, 1/4 of a grain, was given. One hour later the respirations became very shallow, and he died in five minutes.

Post-mortem examination. Heart weight, 490 g. Right ventricle greatly hypertrophied. Coronary arteries normal. Pulmonary artery atheromatous, with a circumference twice that of the aorta. Aorta normal. Lungs very œdematous, with diffuse emphysema.

Case 3. (Communicated by Dr. Macoun.) Male, aged 43. He complained of dyspnœa on exertion for eighteen months. He had a severe high right thoracic kyphoscoliosis which had not prevented him pursuing his occupation as gardener until shortly before admission, when the dyspnœa became so severe that he could not continue. He then had no evidence of congestive failure. Pulse rate 90, with ventricular extrasystoles. Blood pressure 140/100. Apex beat displaced four-and-a-half inches from the midline in the fourth intercostal space. Cardiac dullness to the right of the sternum. Heart sounds normal, and no murmurs. He was treated by rest in bed, mercurial diuretics, and theominal, and responded sufficiently well for him to be discharged to light work in four weeks. Four weeks later, he was precipitated into failure by a mild bronchitic attack. He was then moderately cyanosed. Pulse rate, 100, regular. Respirations 26. Temperature normal. Hepatic enlargement, and œdema of the ankles. Rhonchi heard over both lungs. Treatment again consisted of bed, rest, and mercurial diuretics, with some improvement. He was having restless nights, but in view of the experience of the first two cases, it was decided to give a small dose of morphia, 1/12 of a grain, before resorting to more usual dosage. The respirations became greatly depressed, and he died in one-and-a-quarter hours.

Post-mortem examination. Heart weight, 460 g. Right ventricular wall hypertrophied and dilated. Atheroma at origin of left anterior descending coronary artery. Circumference of pulmonary artery at upper level of valves, 8·2 cm. Circumference of aorta, 6·5 cm. No atheroma of pulmonary artery and only one small patch in aorta. Both lungs very small, with emphysema at borders. Bronchi congested and œdematous, typical of acute bronchitis.

Discussion

None of these patients had ever had morphia administered before the night of their death. The altered respirations and the times of death indicate that morphia probably played a part. Morphia has to be used with care in cyanosis, but it is common experience that, despite cyanosis, many cardiac patients react very favourably to its use. It is therefore reasonable to assume that severe kyphoscoliosis and the associated intrathoracic abnormalities have a bearing on this idiosyncrasy.

Trendelenberg (1926), remarking on morphine in kyphoscoliosis, stated: "Whereas, when the usual therapeutic amounts are given to people with unrestrained breathing, the crippling is usually shown only in a dulling of the breathing, and moderate diminution of breathing volume; in people with restrained breathing (dyspnœa following foreign body in the air passages, abnormal thoracic structure, etc.) even the usual therapeutic doses can so severely deteriorate the pulmonary ventilation through central effect on the breathing centre that life is threatened. In such cases, therefore, morphine should be used with the greatest care."

Chapman, Dill, and Graybiel describe the case of a girl, aged 29, with a severe high right kyphoscoliosis, who was given 1/3 of a grain of pantopon before an operation. Within a few minutes she became so cyanosed and dyspnœic that she had to be placed in an oxygen tent, and her condition remained critical for eight days.

Schroeder described an eclamptic patient whose respirations were depressed to between 2 and 3 a minute after the administration of 1/6 of a grain of morphia.

Severe kyphoscoliotic patients, even in the absence of cardiac failure, have greatly reduced vital capacities. In six such adult patients I have obtained values varying from 850 to 1850 c.c.

In the case of Chapman, Dill, and Graybiel, mentioned above, it was only 560 c.c. Once cardiac failure has supervened, the values will certainly be less. Any event that still further reduces pulmonary function, such as pulmonary infections, or the use of respiratory depresants, is quite sufficient to cause death. Cases 1 and 2, uncomplicated by infection, died after 1/4 of a grain of morphia. Case 3, complicated by infection, could not survive 1/12 of a grain. It is therefore suggested that morphia has no place in the treatment of heart failure consequent upon kyphoscoliosis.

Summary

Three cases are described of severe kyphoscoliosis and cardiac failure who died after the administration of morphia in small dosage. Reference is made to two cases, reported previously by others, who were precipitated into crises by respiratory depresants.

My thanks are due to Sir Maurice Cassidy for permission to publish Cases 1 and 2, and to Dr. Stephen Macoun for the details of Case 3.

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TRANSIENT HEART BLOCK AND CORONARY OCCLUSION IN PLEURAL SHOCK

BY

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Pleural shock is, happily, a rare accident. Anderson (1936) estimates that it occurs once in 2000 refills, and that the fatality rate may vary from 15 to 50 per cent. Ormond (1942), reviewing the reported cases, considers it less common. Be that as it may, it is an alarming happening.

This case, in which syncope occurred during an attempted artificial pneumothorax induction, has unusual features; and some explanation of what occurred will be attempted, though no final conclusions can be drawn.

Case Notes

An attempt was made to induce an artificial pneumothorax in a woman of 24 with tuberculous infiltration of the left upper lobe. The two layers of pleura were found to be adherent, so the attempt was abandoned and she was returned to the ward. A few minutes later she complained of faintness and difficulty in breathing; she became pale, cold, and clammy, with cyanosed lips and dilated pupils; and soon she was unconscious. The respirations were deep and sighing, and the neck veins moderately distended; the pulse could not be felt at the wrist and auscultation showed a slow heart rate. Fig. 1A, taken at this stage, showed complete heart block with a ventricular rate of 44. Atropine sulph., 1/100 of a grain, was given intravenously, and the pulse rate increased in four minutes to 120 a minute. After fifteen minutes Fig. 1B showed normal rhythm at a rate of 65 a minute. Clinical improvement quickly followed the increase in her pulse rate. She soon regained consciousness and in about an hour she seemed reasonably well again. At no time, then or later, did she complain of pain. Five weeks later another electrocardiogram was taken: this, surprisingly, showed strong evidence of a T I type of coronary occlusion. Subsequent records were typical of what might be expected in the gradual return of a coronary curve towards normal. Five months after her attack, she was transferred to a sanatorium in another part of the county with a view to thoracoplasty, but this was not done, and she has since died of pulmonary tuberculosis. This, therefore, seems to be an example of pleural shock with subsequent coronary damage.

Discussion

Pleural Shock. This has been attributed either to a vagal reflex or to air embolism. Opinions differ as to which is the more common and important cause. Cocke (1931, 1935), for instance, considers that it is most commonly a reflex syncope, while Rukstinat (1931) believes that the symptoms are generally the result of air embolism. Forbes (1944), quoting Hamilton and Rothstein, and Chase, in support of his opinion, agrees with Rukstinat. It is evident, however, as Ormond (1942) concludes, that there are two forms of pleural shock—one being a reflex syncope and the other due to air embolism. The former appears to resemble, clinically, an ordinary fainting attack such as has been discussed recently in blood donor clinics. (M.R.C. Report, 1944). That the latter does occur there can be no doubt, the evidence being the cases that have been reported with cerebral symptoms and hemiplegia.

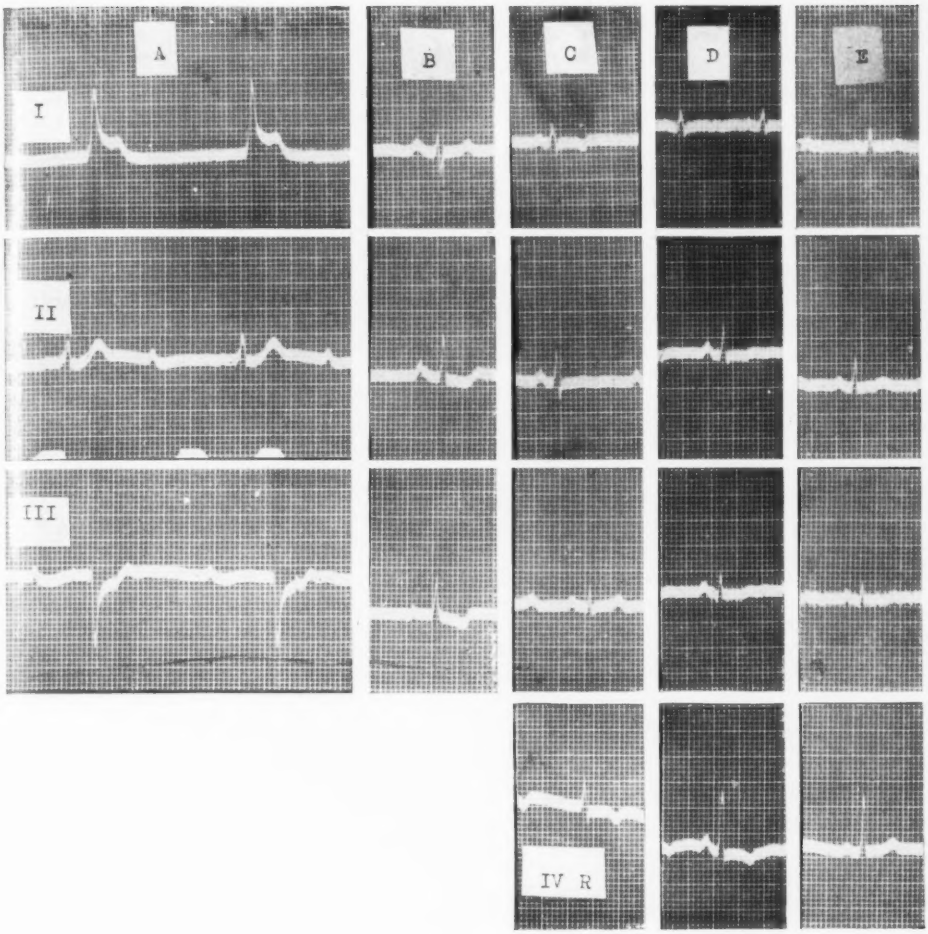

FIG. 1.

(A) 19/6/44. Complete heart block, ventricular rate 44, auricular rate 98. Bizarre QRS–T complex in leads I and III. QRS II, 0·08 sec., S–T II depressed 0·5 mm., T positive, 3·5 mm. (B) 19/6/44, fifteen minutes later. Resumption of normal rhythm, rate 65; P–R interval, 0·2 sec.; right axis deviation, and T III inverted. (C) 28/7/44. Development indicating occlusion of anterior coronary, T I, type. (D) 12/9/44. Regression. T I now flat, T IV still inverted. (E) 17/10/44. T I and T IV now upright, low voltage in limb leads.

the post-mortem demonstration of air in the cerebral and, sometimes, in the coronary arteries, and the clinical signs of air embolism occasionally seen during life in the retinal arteries.

Complete Heart Block. This is most often due to an intrinsic myocardial lesion (Parkinson, Papp, and Evans, 1941), though rarely, as described by Weiss and Ferris (1934), it may be reflex. Comeau (1937), discussing paroxysmal complete block, attributes most cases to coronary sclerosis. There may, again, be a contributory vagal factor as well as a basis of sclerosis, as in Starling's (1921) case which Comeau quotes; here Stokes-Adams seizures were arrested by atropine.

It is possible, therefore, that in my case, as normal rhythm was quickly restored after atropine, some vagal factor was present; yet it must be admitted that normal rhythm might have been resumed in any case.

It is well known (Katz 1941, and others), that complete heart block may mark the onset of

an acute coronary occlusion. It is doubtful whether atropine would restore normal rhythm in those circumstances.

Coronary Embolism. The great majority of acute coronary occlusions must be due to thrombosis. A number of cases caused by various emboli has been collected and extended by Porter and Vaughan (1940). No mention of air embolism is made. In all the cases they describe, præcordial pain was a feature, and a cardiogram of one of them shows a T I type of coronary curve.

Durant (1934), however, describes a probable case of coronary air embolism, with cardiographic evidence of a T I type of coronary occlusion. Here some complaint of substernal oppression was made, but syncope and a generalized convulsion were the most prominent features.

Summary

In the case here described, heart block existing during the acute phase may have been due partly to a vagal reflex, yet a more important factor, from the subsequent cardiogram would appear to have been a coronary occlusion. The possibility of acute coronary insufficiency without occlusion, as described by Master (1944), is not a likely one; his cardiograms do not resemble those here described. It is hardly likely that a coincident coronary thrombosis took place. The close association with the attempted pneumothorax induction, together with the age of the patient, make this extremely unlikely. A wound of the heart can be excluded: the needle was never deep enough to have produced this. A clot disturbed from a thrombotic process in the pulmonary circulations might produce an embolism (Saphir, 1933) and this remains a possibility. It seems more reasonable to assume that an air embolism occurred.

Fig. 1B shows, curiously, right axis deviation, without a coronary type of curve. As the typical changes indicative of coronary occlusion may take some little time to develop—up to a few hours (White, 1931)—this right axis deviation may have existed before the accident, as in Durant's case. Fig. 1C, D, and E leave little doubt that recovery was taking place from myocardial infarction.

An interesting point is the absence of pain. Pain is evidently not one of the main features of this form of pleural shock. It may be that this absence of pain is a clinical characteristic of coronary air embolism, in contradistinction to other types of occlusion.

Heart block may occur more commonly in pleural shock than is thought, and Cocke remarks on bradycardia in two of his cases.

It is suggested that in the case here reported, coronary air embolism occurred producing transient heart block and myocardial infarction.

I have to thank Dr. John Parkinson for many helpful suggestions about this case.

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